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(54) Title: INDOLE DERIVATIVES WITH ANTIVIRAL ACTIVITY

(57) Abstract

The present invention relates to certain indole derivatives, salts, esters and physiologically functional derivatives thereof, to their use in medical therapy and in particular to their use for the manufacture of a medicament for the treatment or prophylaxis of at least one viral infection, for example, herpes virus, retrovirus, hepatitis B virus, coxsackie virus and hepatitis C virus infections.

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INDOLE DERIVATIVES WITH ANTIVIRAL ACTIVITY

The present invention relates to certain indole derivatives, salts, esters and physiologically functional derivatives thereof, to their use in medical therapy and in particular to their use in the manufacture of a medicament for the treatment or prophylaxis of viral infections.

Of the DNA viruses, those of the herpes group are the sources of the most common viral illnesses in man. The group includes herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV); Epstein-Barr virus (EBV) and human herpes virus 6 (HHV6). HSV 1 and HSV 2 are some of the most common infectious agents of man. Most of these viruses are able to persist in the host's neural cells; once infected, individuals are at risk of recurrent clinical manifestations of infection which can be both physically and psychologically distressing.

HSV infection is often characterised by extensive and debilitating lesions of the skin, mouth and/or genitals. Primary infections may be subclinical although tend to be more severe than infections in individuals previously exposed to the virus. Ocular infection by HSV can lead to keratitis or cataracts thereby endangering the host's sight. Infection in the newborn, in immunocompromised patients including AIDS patients or penetration of the infection into the central nervous system can prove fatal.

Transmission of the virus is by direct physical contact between a host and a recipient; the spread of HSV infection is therefore considered a very significant social problem, particularly as no effective vaccine is yet available.

Varicella zoster (VZV) is a herpesvirus which causes chickenpox and shingles. Chickenpox is the primary disease produced in a host without immunity and in young children is usually a mild illness

characterised by a vesicular rash and fever. Shingles or zoster is the recurrent form of the disease which occurs in adults who were previously infected with varicella-zoster virus. The clinical manifestions of shingles are characterised by neuralgia and a vescicular skin rash that is unilateral and dermatomal in distribution. Spread of inflammation may lead to paralysis or convulsions. Coma can occur if the meninges becomes affected. In immunodeficient patients VZV may disseminate causing serious or even fatal illness. VZV is of serious concern in patients receiving immunosuppressive drugs for transplant purposes or for treatment of malignant neoplasia and is a serious complication of AIDS patients due to their impaired immune system.

In common with other herpes viruses, infection with CMV leads to a lifelong association of virus and host and, following a primary infection, virus may be shed for a number of years. Congenital infection following infection of the mother during pregnancy may give rise to clinical effects such as death or gross disease (microcephaly, hepatosplenomegaly, jaundice, mental retardation), retinitis leading to blindness or, in less severe forms, failure to thrive, and susceptibility to chest and ear infections. CMV infection in patients who are immunocompromised for example as a result of malignancy, treatment with immunosuppressive drugs following transplantation or infection with Human Immunodeficiency virus may give rise to retinitis, pneumoitis, gastrointestinal disorders and neurological diseases. CMV infection in AIDS patients is a predominant cause or morbidity as, in 50-80% of the adult population, it is present in a latent form and can be re-activated in immunocompromised patients.

Epstein-Barr virus (EBV) causes infectious mononucleosis and hairy leukoplakis, and is also suggested as the causative agent of human cancer, such as nasopharyngeal cancer, immunoblastic lymphoma, Burkitt's lymphoma.

Hepatitis B virus (HBV) is a small DNA containing virus which infects humans. It is a member of the class of closely related viruses known as the hepadnaviruses, each member of which selectively infects either mammalian or avian hosts, such as the woodchuck and the duck.

HBV is a viral pathogen of world-wide major importance. The virus is aetiologically associated with primary hepatocullular carcinoma and is thought to cause 80% of the world's liver cancer. In the United States more than ten thousand people are hospitalised for HBV illness each year, and average of 250 die with fulminant disease. The United States currently contains an estimated pool of 500,000-1-million infectious carriers. Chronic active hepatitis generally develops in over 25% of carriers, and often progresses to cirrhosis. Clinical effects of infection with HBV range from headache, fever, malaise, nausea. vomiting, anorexia and abdominal pains. Replication of the virus is usually controlled by the immune response, with a course of recovery lasting weeks or months in humans, but infection may be more severe leading to persistent chronic liver disease outlined above.

Of the RNA viruses, one group has assumed a particular importance this is the retroviruses. Retroviruses form a sub-group of RNA viruses which, in order to replicate, must first 'reverse transcribe' the RNA of their genome into DNA ('transcription' conventionally describes the synthesis of RNA from DNA). Once in the form of DNA, the viral genome may be incorporated into the host cell genome, allowing it to take advantage of the host cell's transcription/translation machinery for the purposes of replication. Once incorporated, the viral DNA is virtually indistinguishable from the host's DNA and, in this state, the virus may persist for the life of the cell.

A species of retrovirus, Human Immunodeficiency Virus (HIV), has been reproducibly isolated from humans with Acquired Immune Deficiency Syndrome (AIDS) or with the symptoms that frequently precede AIDS. AIDS is an immunosuppressive or immunodestructive disease that predisposes subjects to fatal opportunistic infections. Character-

istically, AIDS is associated with a progressive depletion of T-cells, especially the helper-inducer subset bearing the OKT^4 surface marker. HIV is cytopathic and appears to preferentially infect and destroy T-cells bearing the OKT^4 marker and it is now generally recognised that HIV is the etiological agent of AIDS.

Another RNA virus which has been recognised as the causative agent of an increasingly serious international health problem is the non-A, non-B hepatitis. At least 80% of cases of chronic post-transfusional non-A, non-B hepatitis have been shown to be due to the virus now identified as hepatitis C and this virus probably accounts for cirtually all cases of post-transfusional hepatitis in clinical settings where blood products are screened for hepatitis B. Whereas approximately half of the cases of acute hepatitis C infection resolve spontaneously over a period of months, the remainder become chronic and in many if not all such cases chronic active hepatitis ensues with the potential for cirrhosis and hepatocellular carcinoma. The structure of the hepatitis C virus genome has recently been elucidated and the virus has been characterised as a single stranded RNA virus with similarities to flaviviruses.

Coxsackie viruses belong to the enterovirus genus. They have a single stranded RNA genome contained in an icosachedral nucleocapsid. Coxsackie virus infection is increasingly recognised as a cause of primary myocardial disease in adults and children. Coxsackie infection is also associated with meningitis, pleurodynia, herpangia, hand-feet and mouth disease, respiratory disease, eye disease, diabetes and post-viral fatigue syndrome. In the latter case viral RNA has been detected in the muscle and in menocytes.

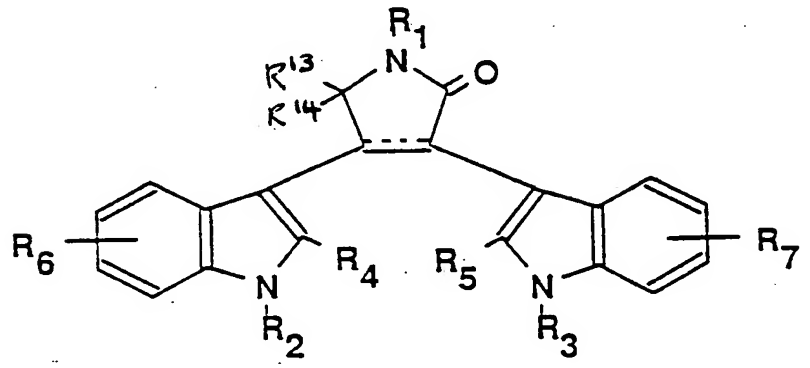
European Patent Specification 0 328 000 describes certain indolecarbozole derivatives and indicates that these compounds can be used for the treatment of heart and blood vessel diseases, such as thrombosis, arteriosclerosis and hypertension, inflammatory processes, allergies, cancers and certain degenerative damage to the central

nervous system. Maleimide derivatives having similar suggested properties are described in European Patent Specification 0 391 060.

US patent 5,043,335 describes certain indolecarbazoles and their use in the method of treating heart and blood vessel diseases such as thromboses, arteriosclerosis and hypertension.

We have now identified certain indole derivatives which have unexpectedly been found suitable for use in the treatment or prophylaxis of viral infections, in particular retrovirus, herpesvirus and hepatitis viral infections.

The present invention lies in the use of a compound of formula (I)



(I)

wherein

the dotted line represents an optional bond;

R^1 represents:

-H;

$-COR^{10}$, $-COOR^{10}$ where R^{10} is C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl (for example phenyl), arylalkyl (for example benzyl), C_{1-6}alkenyl, or H;

$-OR^{10}$ wherein R^{10} is as hereinbefore defined;

$-C_{1-8}$alkyl, C_{1-8}alkenyl or C_{3-8}cycloalkyl where the alkyl, alkenyl or cycloalkyl moiety may be optionally substituted by one or more substituents selected from halogen, cyano, nitro, azido, $-OR^{10}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-NR^{11}R^{12}$ (where R^{11} and R^{12}, which may be the same or different, each represent H, $-COR^{10}$ where R^{10} is as hereinbefore defined, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylalkyl, tetrahydronaphthyl or indanyl or $-R^{11}R^{12}$ together with the N atom to which they are attached form a 3-,4-,5- or 6- membered heterocyclic ring (for example piperidine, pyrrolidine) in which from 1 to 3 of the carbon atoms may be replaced by heteroatoms independently selected from O, N and S (for example, morpholino, piperazine) which ring

being, where possible, partially or completely unsaturated), $T-\overset{\overset{Z}{\|}}{C}-W$ (where T is NH or S, Z is NH, S or O and W is $NR^{11}R^{12}$ where R^{11} and R^{12} are each as defined above), non-aromatic heterocycle, -NH-non-aromatic-heterocycle and aryl groups, such heterocycle or aryl groups being optionally substituted by one or more substituents selected from $-OR^{10}$, $-NR^{11}R^{12}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-CO_2R^{10}$, nitro, cyano, SCN, C_{1-6}alkyl (wherein one or more hydrogen atoms are optionally replaced by a halogen atom (for example trifluoromethyl)), C_{3-6} cycloalkyl, hydroxyC_{1-6}alkyl, $CONH_2$, halogen and methylenedioxy, where R^{10}, R^{11} and R^{12} are each as defined above;

$-NR^{11}R^{12}$ where R^{11} and R^{12} are each as defined above;

-aryl (for example phenyl) optionally substituted by one or more substituent(s) selected from OR^{10}, $-NR^{11}R^{12}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-CO_2R^{10}$, nitro, cyano, SCN, C_{1-6}alkyl, C_{3-6}cycloalkyl, haloalkyl, hydroxyC_{1-6}alkyl, $CONH_2$, halogen and methylenedioxy, where R^{10}, R^{11} and R^{12} are each as defined above;

- a cyclic group containing from 3 to 6 carbon atoms in which from 1 to 3 of said atoms may be replaced by heteratom(s) independently selected from O, S and N (for example thiazole, pyrazole, imidazole, triazole, oxazole, piperidine);

-NH-cyclic group containing from 3 to 6 carbon atoms in which from 1 to 3 of said atoms may be replaced by heteratom(s) independently selected from O, S and N (for example thiazole, pyrazole, imidazole, triazole, oxazole, piperidine);

R^2 and R^3, which may be the same or different, are each independently selected from:-

H;

$-COR^{10}$, $-COOR^{10}$ where R^{10} is a C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl (for example phenyl), arylalkyl (for example benzyl), C_{1-6}alkenyl, or H;

$-OR^{10}$ wherein R^{10} is as hereinbefore defined;

$-C_{1-8}$alkyl, C_{1-8}alkenyl or C_{3-8}cycloalkyl where the alkyl, alkenyl or cycloalkyl moiety may be optionally substituted by one or more substituents selected from halogen, cyano, nitro, azido, C_{3-8}cycloalkyl $-OR^{10}$, $-CO_2R^{10}$, $-OCOR^{10}$, $-SR^{10}$, $-SOR^{10}$, SO_2R^{10}, $-CO_2NR^{11}R^{12}$, $-NR^{11}R^{12}$ (where R^{11} and R^{12}, which may be the same or different, each represent H, $-COR^{10}$ where R^{10} is as hereinbefore defined, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylalkyl, tetrahydronaphthyl or indanyl or $-R^{11}R^{12}$ together with the N atom to which they are attached form a 3-,4-,5- or 6- membered heterocyclic ring (for example piperidine, pyrrolidine) in which from 1 to 3 of the carbon atoms may be replaced by heteroatoms independently selected from O, N and S (for example, morpholino, piperazine) which ring being where possible, partially or completely unsaturated); $-T-\overset{Z}{\overset{\|}{C}}-W$ (where T is NH or S, Z is NH, S or O and W is $NR^{11}R^{12}$ where R^{11} and R^{12} are each as defined above), non-aromatic heterocycle, -NH-non-aromatic-heterocycle and aryl, such heterocycle or aryl groups being optionally substituted by one or more substituents selected from $-OR^{10}$, $-NR^{11}R^{12}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-CO_2R^{10}$, nitro, cyano, SCN, C_{1-6}alkyl (wherein one or more hydrogen atoms are optionally replaced by a halogen atom

(for example trifluoromethyl)), C_{3-6} cycloalkyl, hydroxylC_{1-6}alkyl, $CONH_2$, halogen and methylenedioxy, where $R^{10}R^{11}$ and R^{12} are each as defined above);

$-NR^{11}R^{12}$ where R^{11} and R^{12} are each as defined above;

-aryl (for example phenyl) optionally substituted by one or more substituent(s) selected from $-OR^{10}$, $-NR^{11}R^{12}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, CO_2R^{10}, nitro, cyano, SCN, C_{1-6}alkyl (wherein one or more hydrogen atoms are optionally replaced by a halogen atom (for example trifluoromethyl)), C_{3-6}cycloalkyl, hydroxyC_{1-6}alkyl, $CONH_2$, halogen and methylenedioxy, where R^{10}, R^{11} and R^{12} are each as defined above;

R^4 and R^5, which may be the same or different, are each independently selected from:

H;

$-C_{1-6}$alkyl or C_{3-7}cycloalkyl (where the alkyl moiety may be optionally substituted by one or more substituent(s) selected from $-OR^{10}$ $-NR^{11}R^{12}$, where R^{10}, R^{11} or R^{12} are as defined above, halogen and aryl);

-aryl optionally substituted by one or more substituent(s) selected from $-OR^{10}$, $-NR^{11}R^{12}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-CO_2R^{10}$, nitro, cyano, SCN, C_{1-6}alkyl (wherein one or more hydrogen atoms are optionally replaced by a halogen atom (for example trifluoromethyl)), C_{3-6}cycloalkyl, hydroxyC_{1-6}alkyl, $CONH_2$, halogen and methylenedioxy, where $R^{10}R^{11}$ and R^{12} are each as defined above;

R^6 and R^7, which may be the same or different, each represent one or more ring substituent(s) selected from:

H;

$-C_{1-6}$alkyl optionally substituted by one or more substituents independently selected from halogen (for example trifluoromethyl), $-NR^{11}R^{12}$, cyano, $-OR^{10}$, azido, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$ wherein R^{10}, R^{11} and R^{12} are as hereinbefore defined.

-cyano, nitro, halogen, methylenedioxy, $-OR^{10}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-NHSO_2R^{10}$, $-SO_2NR^{11}R^{12}$, $-CO_2R^{10}$, $-OCOR^{10}$, $-CONR^{11}R^{12}$ and $-NR^{11}R^{12}$ where R^{10}, R^{11} and R^{12} are as defined above;

R^{13} and R^{14} together form a carbonyl group (>=O) or R^{13} is X and R^{14} is Y and X and Y are both H, or one of X and Y is H and the other is $-OR^{10}$ or $-SR^{10}$, wherein R^{10} is as hereinbefore defined;

or a salt, ester or physiologically functional derivative thereof or a solvate of any thereof, for the manufacture of a medicament for the treatment or prophylaxis of at least one viral infection. Such viral infections include a retrovirus infection, for example HIV, a herpes virus infection, such as those mentioned above and more particularly CMV, VZV, HSV1 and HSV2 or an HBV infection.

The present invention also provides the use of the compounds of formula (I) for the manufacture of a medicament for the treatment or prophylaxis of a coxsackie virus or hepatitis C virus infection.

As used herein, the term "alkyl" as a group or part of a group means a straight or branched chain alkyl group. Such alkyl groups preferably have 1 to 3 carbon atoms. As used herein the term aryl as a group or part of a group includes aromatic heterocycles (such as pyridino, pyrrolo, furyl, thienyl, pyrazolo, imidazolo, thiazolo, isothiazolo, oxazolo, triazolo, tetrazolo, oxadiazolo, thiadiazolo, benzofuryl, benzothienyl, benzimidazolo, benzotriazolo, quinolyl, isoquinolyl and indolyl). The term non-aromatic heterocycle includes groups such as pyrrolidino, piperazino, morpholino, piperidino, tetrahydrofuryl, tetrahydropyranyl, dioxanyl and dithianyl.

The compounds of formula (I) described above and their salts, esters and physiologically functional derivatives and the solvates of any thereof are hereinafter referred to as the compounds according to the invention.

Examples of retroviral infections which may be treated or prevented in accordance with the invention include human retroviral infections such as Human Immunodeficiency Virus (HIV), for example, HIV-1 or HIV-2, and Human T-cell Lymphotropic Virus (HLTV), for example, HTLV-I or HTLV-II, infections. The compounds according to the invention are especially useful for the treatment of AIDS and related clinical conditions such as AIDS-related complex (ARC), progressive generalized lymphadenopathy (PGL), Kaposi's sarcoma, thrombocytopenic purpura, AIDS-related neurological conditions, such as multiple sclerosis or tropical paraperesis, and also anti-HIV antibody-positive and HIV-positive conditions, including such conditions in asymptomatic patients.

Examples of other clinical conditions which may be treated in accordance with this invention include those conditions caused by HIV, HSV 1 and 2, VZV, CMV, EBV, HHV6, HBV, coxsackie virus or hepatitis C virus infections as described above.

The present invention further includes a method for the treatment, prophylaxis or prevention of the symptoms or effects of a viral infection in an infected host, for example, a mammal including humans, which comprises administering to said host a therapeutically effective non-toxic amount of a compound according to the invention. According to a particular embodiment of this aspect of the invention, the viral infection is a retrovirus, for example, HIV, herpes virus including HSV 1 and 2, VZV, CMV, EBV, HHV6, an HBV, coxsackie virus or hepatitis C virus infection.

Certain of the compounds according to the invention are new and such new compounds are a further aspect of the present invention. The new compounds of formula (I) include:

(i) a compound of formula (I) wherein the dotted line does not represent a bond; or a salt, ester or physiologically functional derivative thereof or a solvate of any thereof, excluding the compounds:-

(a) Cis-3,4-bis-(1H-indol-3-yl)-2,5-pyrrolidinedione

(b) Trans-3,4-bis-(1H-indol-3-yl)-2,5-pyrrolidinedione;

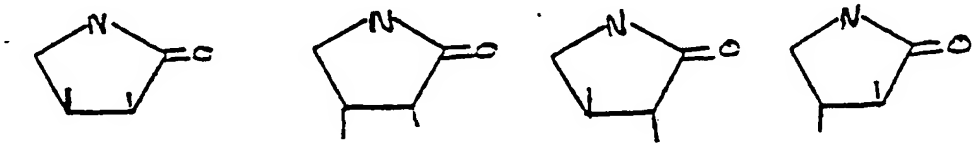
(ii) a compound of formula (I) wherein R^{13} is X and R^{14} is Y and one of X and Y is H and the other is $-OR^{10}$ (excluding OH) or $-SR^{10}$, wherein R^{10} is as hereinbefore defined;

and

(iii) a compound of formula (I) wherein the dotted line represents a bond, R^1 is H or C_{1-8}alkyl optionally substituted by one or more substituents selected from $-OR^{10}$ wherein R^{10} is as hereinbefore defined and aryl optional substituted by one or more substituents selected from C_{1-6}alkyl wherein one or more hydrogen atoms are replaced by a halogen atom and $-NR^{11}R^{12}$ wherein R^{11} and R^{12} are as hereinbefore defined; R^2 and R^3, which may be the same, or different, are each independently selected from H and C_{1-8}alkyl substituted by one or more substituents selected from $-OR^{10}$, $-OCOR^{10}$ wherein R^{10} is as hereinbefore defined, C_{3-8}cycloalkyl and aryl optionally substituted by one or more substituents selected from haloalkyl and $-OR^{10}$ wherein R^{10} is as hereinbefore defined; R^4 and R^5 which may be the same or different, are each independently selected from H and C_{1-6}alkyl; R^6 and R^7, which may be the same or different, each represent one or more ring substituent(s) selected from H, C_{1-6}alkyl, $-OR^{10}$ wherein R^{10} is

as hereinbefore defined and halogen and R^{13} and R^{14} together form a carbonyl group; or a salt, ester or physiologically acceptable derivative thereof or a solvate of any thereof; excluding the compound 3,4-bis-1H-indol-3-yl-1-(phenylmethyl)-1H-pyrrole-1,5-dione; the new compounds of formula (I) are hereinafter referred to collectively as compounds of formula (IA).

It will be appreciated that when the dotted line does not represent a bond, the compound of formula (I) may exist as both "cis" (wherein the indolyl groups are located on the same side of the bond) and "trans" (wherein the indolyl groups are located on opposte sides of the bond) isomers. It will also be appreciated that in view of the asymmetry of the pyrrolidone ring, the cis and trans isomers can each exist in two forms, viz



The present invention covers each of the four isomers and any combination of two or more thereof.

The preferred compounds of formula (IA) include:-

3,4-Bis(7-methyl-1H-indol-3-yl)2,5-dihydro-1H-pyrrolo-2,5-dione;

3,4-Bis(4-fluoro-1H-indol-3-yl)2,5-dihydro-1H-pyrrolo-2,5-dione;

3,4-Bis(5-methoxy-1H-indol-3-yl)-2,5-dihydro-1-(3-trifluoromethyl-phenylmethyl)-1H-pyrrolo-2,5-dione;

3,4-Bis(1H-indol-3-yl)-2,5-dihydro-1-(benzyloxymethyl)-1H-pyrrolo-2,5-dione;

3,4-Bis(6-fluoro-1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

3,4-Bis(1H-indol-3-yl)-2,5-dihydro-1-(4-dimethylaminophenylmethyl)-1H-pyrrolo-2,5-dione;

3,4-Bis(1H-indol-3-yl)-2,5-dihydro-1-(2-pyridylmethyl)-1H-pyrrolo-2,5-dione;

Cis-3,4-Bis(2-methyl-1H-indol-3-yl)-1-(phenylmethyl)-succinimide;

3-(1-Cyclohexylmethyl-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

3-(1-(3-Acetoxypropyl)-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

3-(1-(3-Methoxypropyl)-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

3-(1-(3-Phenoxyphenylmethyl)-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

or a salt, ester or a physiologically functional derivative thereof or a solvate of any thereof.

The present invention also includes the compounds of formula (IA) for use in medical therapy, particularly as antiviral agents.

It will be understood that each of the preferred compounds of formula (IA) above is particularly efficacious in the treatment or prophylaxis of at least one viral infection independently selected from those of HSV1, HSV2, CMV, VZV,EBV, HHV6, HBV, HIV, hepatitis C virus and coxsackie virus.

The present invention also provides 3,4-bis-(1H-indol-3-yl)-1-(phenylmethyl)-2,5-pyrrolidinedione and cis-3,4-bis(1H-indol-3-yl)-2,5-pyrrolidinedione; or a salt, ester or physiologically functional derivative thereof or a solvate thereof, for use in therapy, particularly in the treatment or prophylaxis of viral infections, for example a herpes virus infection such as those mentioned above and more particularly CMV, HSV 1 and 2 and VZV, a retroviral infection for example HIV and a heptatis infection including HBV.

In addition to the use of compounds of formula (I) including compounds of formula (IA), in the treatment or prophylaxis of the above viral infections and associated conditions, the compounds may also be used for the treatment or prophylaxis of heart and blood vessel diseases, such as thromboses, arteriosclerosis and hypertension, inflammatory processes, allergies, cancers and certain degenerative damage to the central nervous system.

As used herein, the term "physiologically functional derivative" means any physiologically acceptable salt, ester, or salt of such ester, of a compound of formula (I) or (IA) above or any other compound which upon administration to the recipient, is capable of providing (directly or indirectly) such a compound or an antivirally active metabolite or residue thereof. For example, it is within the scope of the invention to replace the H of an OH group by a potentially hydrolysable group such as acyl or alkyl.

Preferred esters in accordance with the invention include carboxylic acid esters in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, methyl, n-propyl, t-butyl, or n-butyl), cycloalkyl, alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy), or amino; sulphonate esters, such as alkyl- or aralkylsulphonyl (for example, methanesulphonyl); amino acid esters

(for example, L-valyl or L-isoleucyl); and mono-, di-, or tri-phosphate esters. In such esters, unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group. Any reference to any of the above compounds also includes a reference to a physiologically acceptable salt thereof.

Examples of physiologically acceptable salts of the compounds of formula (I) and physiologically acceptable derivatives thereof include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C_{1-4}alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulphonic, ethanesulphonic, benzenesulphonic and p-toluenesulphonic acids, and inorganic acids, such as hydrochloric, sulphuric, phosphoric and sulphamic acids. Physiologically acceptable salts of a compound of an hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+, NH_4^+ and NX_4^+ (wherein X is a C_{1-4} alkyl group).

For therapeutic use, salts of compounds of formula (I) or (IA) will be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

The compounds according to the invention may be employed alone or in combination with other therapeutic agents for the treatment of the above infections or conditions. Combination therapies according to the present invention comprise the administration of at least one compound of the formula (I) or (IA) or a physiologically functional derivative thereof and at least one other pharmaceutically active ingredient. The active ingredient(s) and pharmacologically active agent(s) may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order. The amounts of the active ingredient(s) and pharmacologically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Preferably the combination therapy involves the administration of one compound of the formula (I) or (IA) or a physiologically functional derivative thereof and one of the agents mentioned herein below.

Examples of such further therapeutic agents include agents that are effective for the treatment of HIV infections or associated conditions such as 3'-azido-3'-deoxythymidine (zidovudine), other 2',3'-dideoxy-nucleosides such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine and 2',3'-dideoxyinosine, carbovir, acyclic nucleosides (for example, acyclovir), 2',3'-didehydrothymidine, protease inhibitors such as N-tert-butyl-dechydro-2-[-2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolyl-carbonyl)-L-asparginyl]butyl]-(4aS,8aS)- isoquinoline-3(S)-carboxamide (Ro 31-8959), oxathiolan nucleoside analogues such as cis-1-(2-hydroxymethyl)-1,3-oxathiolan-5-yl)-cytosine or cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluoro-cytosine, 3'-deoxy-3'-fluoro- thymidine, 2',3'-dideoxy-5-ethynyl-3'-fluorouridine, 5-chloro-2'3'-dideoxy-3' fluorouridine, Ribavirin, 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]guanine(H2G), TAT inhibitors such as 7-chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2(H)-one (Ro5-3335), or 7-chloro-1,3-dihydro-5-(1H-pyrrol-2-yl)-3H-1,4-benzodiazepin-2-amine (Ro24-7429) interferons such as α-interferon, renal excretion inhibitors such as probenecid, nucleoside transport inhibitors such as dipyridamole; pentoxifylline,

NAcetylCysteine, Procysteine, α-trichosanthin, phosphonoformic acid, as well as immunodulators such as interleukin II, granulocyte macrophage colony stimulating factors, erythropoetin, soluble CD_4 and genetically engineered derivatives thereof. Examples of such further therapeutic agents which are effective for the treatment of HBV infections include carbovir, oxathiolan nucleoside analogues such as cis-1-(2-hydroxymethyl)-1,3-oxathiolan-5-yl)-cytosine or cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl-5-fluoro-cytosine, 2',3'-dideoxy-5-ethynyl-3'-fluorouridine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, 1-(β-D-arabinofuranosyl)-5-propynyluracil, acyclovir and interferons, such as α interferon.

More preferably the combination therapy involves the administration of one of the above-mentioned agents together with one of the compounds of formula (I) or (IA) specifically named herein.

The present invention further provides pharmaceutical formulations containing pharmaceutically acceptable compounds according to the invention, also referred to herein as active ingredients, which may be administered for therapy to a mammal including a human ("the recipient") by any suitable route appropriate to the clinical condition to be treated; suitable routes include oral (including buccal and sublingual), pulmonic, rectal, nasal, topical (including buccal, sublingual and transdermal), vaginal and parenteral (including subcutaneous, intramuscular, intravenous and intradermal). It will be appreciated that the preferred route will vary with the condition, weight, age and sex of the recipient, the nature of the infection and the chosen active ingredient.

The amount of a compound according to the invention required for the treatment of each of the above indicated utilities and indications will depend on a number of factors including the severity of the condition to be treated and the identity of the recipient and will ultimately be at the discretion of the attendant physician.

In general, however, for each of these utilities and indications, a suitable, effective dose will be in the range 0.5 to 120 mg per kilogram body weight of the recipient per day, preferably in the range 1 to 90 mg per kilogram body weight per day and most preferably in the range 2 to 60 mg per kilogram body weight per day. An optimum dose is about 30 mg per kilogram body weight per day. Unless otherwise indicated all weights of active ingredients are calculated as the parent compounds of the compounds according to the invention. In the case of a salt, ester or physiologically functional derivative of a compound according to the invention or a solvate of any thereof the figures would be increased proportionately. The desired dose is preferably presented as two, three, four, five, six, or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing from 1 to 1500 mg, preferably from 5 to 1000 mg, most preferably from 10 to 700 mg of active ingredient per unit dosage form. Alternatively, if the condition of the recipient so requires, the dose may be administered as a continuous infusion.

Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.25 to about 100 μM, preferably from about 0.5 to 70 μM, most preferably from about 1 to about 50 μM. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% w/v solution of the active ingredient, optionally in saline, or orally administered, for example, as a tablet, capsule, or syrup containing from about 0.5 to about 100 mg/kg of the active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide from about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing from about 0.4 to about 15 mg/kg of the active ingredient.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. The formulations of the present invention comprise at least one active ingredient, as defined above, together with one or more acceptable

carriers thereof and, optionally, one or more other therapeutic agents. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

Formulations of the invention include those suitable for administration by any of the aforementioned routes which may conveniently be presented in unit dosage form and may be prepared by any method well know in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary, or paste or may be contained within liposomes.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (for example, povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycollate, cross-linked povidone, crossed-linked sodium carboxmethyl cellulose), or a surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an

inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile or to be soluble or effervescent when added to liquid. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for oral use may also include buffering agents designed to neutralise stomach acidity. Such buffers may be chosen from a variety of organic or inorganic agents such as weak acids or bases admixed with their conjugated salts.

A capsule may be made by filling a loose or compressed powder on an appropriate filling machine, optionally with one or more additives. Examples of suitable additives include binders such as povidone; gelatin, lubricants, inert diluents and disintegrants as for tablets. Capsules may also be formulated to contain pellets or discrete sub-units to provide slow or controlled release of the active ingredient. This can be achieved by extruding and spheronising a wet mixture of the drug plus an extrusion aid (for example microcrystalline cellulose) plus a diluent such as lactose. The spheroids thus produced can be coated with a semi-permeable membrane (for example ethyl cellulose, Eudragit WE30D) to produce sustained release properties.

An edible foam or whip formulation ideally comprises; 50-70% of an edible oil, particularly a vegetable oil, including corn oil, peanut oil, sunflower oil, olive oil and soybean oil; 2-10% of one or more surfactants particularly lecithin, polyols, polyol polymer esters including glyceryl fatty acid esters, polyglyceryl fatty acid esters (e.g. decaglycerol tetraoleate), or sorbitan fatty acid esters (e.g. sorbitan monostearate); 1-4% of a propellant which is suitable for ingestion, notably a compressed gas propellant especially nitrogen, nitrous oxide or carbon dioxide, or a gaseous hydrocarbon especially

propane, butane or isobutane; 0.5-30% of one or more viscosity modifiers of particle size in the range 10-50 microns in diameter, particularly powdered sugars or colloidal silicon dioxide; and optionally 0.5-1% of one or more suitable, non-toxic colourings, flavourings or sweetners. The active ingredient is preferably present in such formulations in a concentration of 10-46%, advantageously 30%. An edible foam or whip formulation as described above may be prepared in a conventional manner, for example by mixing the edible oil, surfactant(s) and any other soluble ingredients, adding the viscosity modifier(s) and milling the mixture to form a uniform dispersion and suspension. The active ingredient is blended into the milled mixture until evenly dispersed. Finally, a metered quantity of propellant is incorporated to the mixture after said mixture has been measured into a suitable dispensing container.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations for topical administration according to the present invention may be formulated as an ointment, cream, suspension, lotion, powder, solution, paste, gel, spray, aerosol or oil. Alternatively, a formulation may comprise a dressing such as a bandage or adhesive plaster impregnated with active ingredients and optionally one or more excipients or diluents.

For infections of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical

ointment or cream containing the active ingredient in an amount of, for example, 0.075 to 20% w/w, preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base or as a water-in-oil base.

If desired, the aqueous phase of the cream base may include, for example, at least 40-45% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulphoxide and related analogues.

The oily phase of an emulsion formulation according to the invention may comprise merely an emulsifier (otherwise known as an emulgent), but desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stablilizer. It is also preferred to include both an oil and a fat. Together, the emulsifer(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulphate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent. The ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10%, particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured material, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert material such as gelatin and glycerin, or sucrose and acacia; and mouth-washes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or higher fatty alcohol (e.g. hard wax, European Pharmacopoeia) or triglycerides and saturated fatty acids (e.g. Witepsol) or as an enema wherein the active ingredient may be presented in an aqueous or oily

solution, an aqueous or oily suspension, an oil-in-water liquid emulsion or water-in-oil liquid.

Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient.

Suitable formulations for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

For pulmonary administration via the mouth, the particle size of the powder or droplets is typically in the range 0.5 - 10μm, preferably 1 - 5μm, to ensure delivery into the bronchial tree. For nasal administration, a particle size in the range 10 - 500μm is preferred to ensure retention in the nasal cavity.

Metered dose inhalers are pressurised aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in liquefied propellant. During use these devices discharge the formulation through a valve adapted to deliver a metered volume, typically from 10 - 150μl, to produce a fine particle spray containing the active ingredient. Suitable propellants include propane and butane, certain chlorofluorocarbon compounds, commonly referred to as "CFS's", for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, or mixtures thereof. The formulation may additionally contain co-solvents, for example ethanol, surfactants such as oleic acid or sorbitan trioleate, antioxidants and/or suitable flavouring agents.

Nebulizers are commercially available devices that transform solutions or suspensions of the active ingredient into an aerosol therapeutic mist either by means of acceleration of a compressed gas through a narrow venturi orifice, typically air or oxygen, or by means of ultrasonic agitation. Suitable formulations for use in nebulizers consist of the active ingredient in a liquid carrier and comprising up to 40%w/w of the formulation, preferably less than 20%w/w. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not prepared sterile, for example methylhydroxybenzoate, antioxidants, flavouring agents, volatile oils, buffering agents and surfactants.

Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in-situ and the powder either presented to air drawn through the device upon inhalation or alternatively delivered by means of a manually operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent such as lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 - 100%w/w of the formulation.

Pressurised aerosol formulations for inhalation are preferably arranged so that each metered dose contains from 0.05 to 5 mg of a compound of the invention. Similarly, powder formulations for insufflations are so arranged that each unit dose contains from 0.5 to 50 mg. Solution or suspension formulations for nebulisation are arranged as to deliver doses between 1 and 1500 mg. The compounds according to the invention or formulations thereof may be administered

by these devices once or several times daily, with one or several doses, for example three or four, being given on each occasion.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

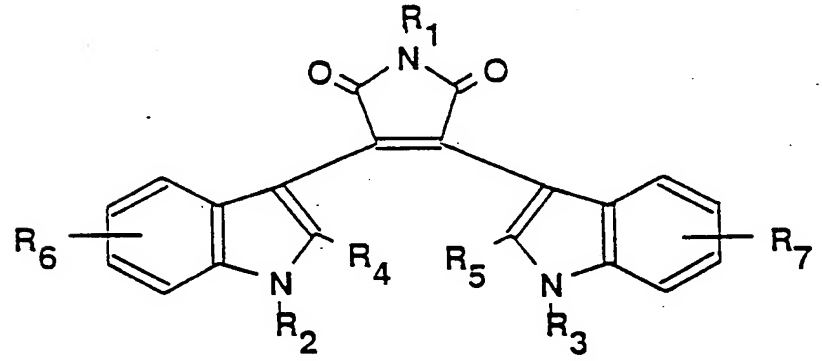
It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

A compound of formula (I) or a salt, ester or physiologically functional derivative of a compound of formula (I) or a solvate of any thereof may be prepared by the general methods outlined below.

In the following description the symbols R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{13}, R^{14}, X and Y have the meanings ascribed to them in formula (I) unless otherwise stated. The symbol $R^{10'}$ represents an alternative value of R^{10}.

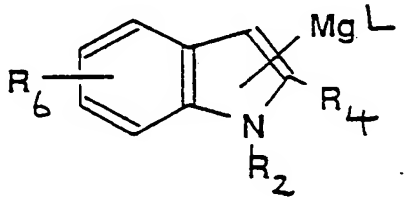
The compounds of formula (I) may be prepared by a process which comprises:-

(A) for the preparation of a compound wherein the dotted line does not represent a bond and R^{13} and R^{14} together form a carbonyl group, by reducing a compound of formula (XVI)

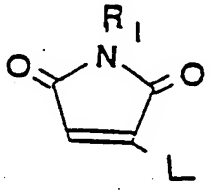


(XVI)

(B) for the preparation of a compound wherein the dotted line does not represent a bond and R^{13} and R^{14} together form a carbonyl group by reacting a compound of formula (XVII) with a compound of formula (XVIII)

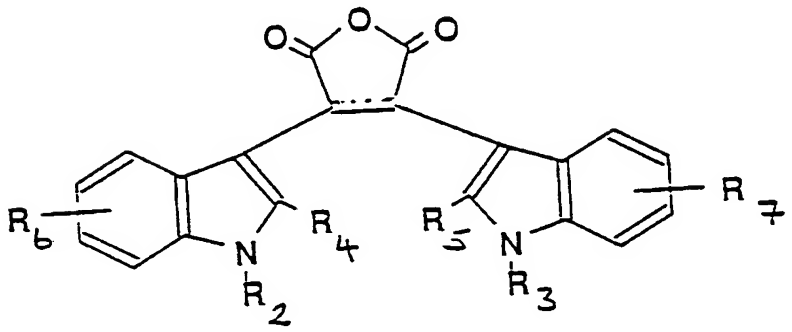


(XVII)



(XVIII)

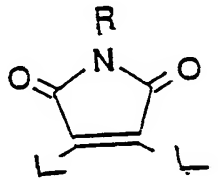
(C) for the preparation of a compound wherein R^{13} and R^{14} together form a carbonyl group, by reacting a compound of formula (XI)



(XI)

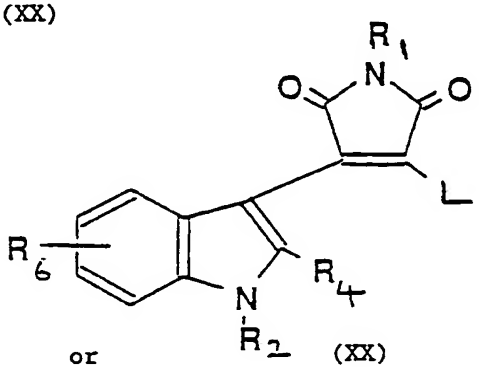
with an amine of formula R^1NH_2 or R^1NH_3X wherein X^1 represents an acid anion.

(D) for the preparation of a compound wherein the dotted line represents a bond and R^{13} and R^{14} together form a carbonyl group, by reacting a compound of formula (XVII) as defined above with a compound of formula (XIX) or (XX)



(XIX)

or



(XX)

(E) for the preparation of a compound wherein X is H and Y is OH, by reducing a compound of formula (I) wherein R^{13} and R^{14} together form a carbonyl group, and optionally converting the compound so formed to a compound wherein X and Y are both H;

(F) for the preparation of a compound wherein X is H and Y is $-OR^{10}$ or $-SR^{10}$, by treating a compound of formula (I) wherein X is H and Y is OH, $-OR^{10'}$ or $SR^{10'}$ with a compound $R^{10}OH$ or $R^{10}SH$;

and thereafter, or simultaneously therewith, effecting one or more of the following optional conversions:-

(i) when the compound of formula (I) is formed, converting it into another compound of formula (I) having different values of R_2, R_3, R_4, R_5, R_6 and R_7 by treatment with an appropriate reagent and/or under suitable conditions;

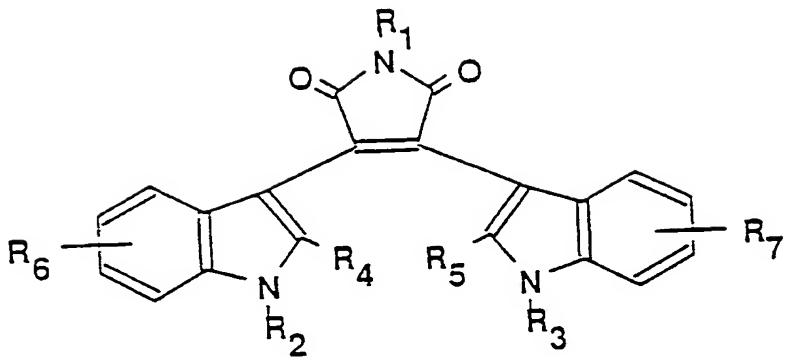
(ii) removing any remaining protecting groups;

(iii) when the compound of formula (I) is formed, converting in into a pharmaceutically acceptable derivative thereof;

(iv) when a pharmaceutically acceptable derivative of a compound of formula (I) is formed, converting the said derivative into a compound of formula (I), or a different derivative thereof.

According to another aspect, the present invention provides a process for the preparation of a compound of formula (IA) or a salt, ester or physiologically functional derivative thereof or a solvate of any thereof in accordance with the processes described above for the preparation of compounds of formula (I) or a salt, ester or physiologically functional derivative thereof or a solvate of any thereof.

Compounds of formula (I) wherein the dotted line does not represent a double bond and R^{13} and R^{14} together form a carbonyl group may conveniently be prepared by reacting compounds of formula (XVI)

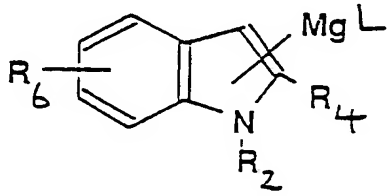


(XVI)

with hydrogen in the presence of a suitable catalyst for example palladium on carbon, palladium black or platinum oxide in a suitable solvent such as acetic acid, tetrahydrofuran, dimethylformamide, or ethanol, and preferably under pressure (eg. 50-300 PSI). Alternative hydrogen donors such as cyclohexadiene, formic acid, and ammonium formate may be used to replace hydrogen.

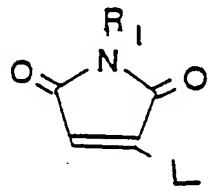
Alternatively, reducing agents such as diimide, or metals such as lithium, sodium, potassium, zinc amalgam or activated zinc in a suitable solvent, such as ethanol, ammonia or combinations thereof may be used to convert (XVI) into (I). Alternatively zinc amalgam or activated zinc, preferably in the presence of acid (for example HCl) in a suitable solvent (for example ethanol) may be used to convert (XVI) into (I).

Compounds of formula (I) wherein the dotted line does not represent a bond may also be prepared by reacting compounds of formula (XVII)



(XVII)

wherein L is a leaving group such as halogen (bromide, chloride, iodide), with a compound of formula (XVIII)



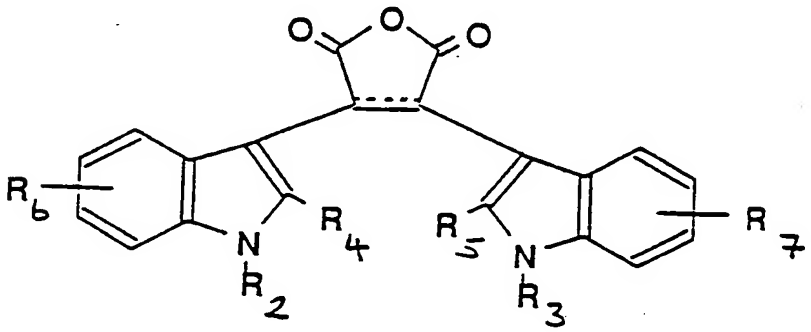
(XVIII)

wherein L is a leaving group as hereinbefore defined, in a suitable solvent for example tetrahydrofuran, diethyl ether, benzene, toluene, or combinations thereof at temperatures in the range 25-140°C, preferably 50-100°C for 30 mins. to 4 days, preferably 1 hour-18h.

Compounds of formula (XVII) may be prepared from the corresponding indole and alkyl or aryl magnesium halide by methods known in the art for example in accordance with the method described by M.Brenner et al, (Tetrahedron (1988) 44, 2887-2892) and B. Sarstedt et al. (Heterocycles (1983) 20, 469-476), P.D. Davis et al. (J.Med.Chem. (1992), 177-184).

Compounds of formula (XVIII) for example bromomaleimide may be prepared according to the method described in Chem. Abstract 1961 55 093738B. (Rend. accad. sci. fis. emat Ser 4 26, 149-53 (1959)).

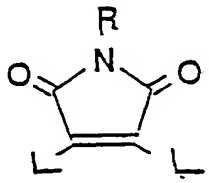
Compounds of formula (XVI) may be prepared by reacting compounds of formula (XI)



(XI)

with an amine of formula R^1NH_2 (R^1 as previously defined) or amine salt of formula $R^1NH_3X^1$ (X^1 signifies an acid anion such as halide, carboxylate, carbonate or sulphate), optionally in a suitable solvent for example tetrahydrofuran, dimethylformamide, acetic acid or toluene, or combinations thereof, or with hexamethyldisilazane and methanol in a suitable solvent such as tetrahydrofuran or dimethylformamide.

Compounds of formula (XVI) may also conveniently be prepared by reacting compounds of formula (XVII) with a compound of formula (XIX)

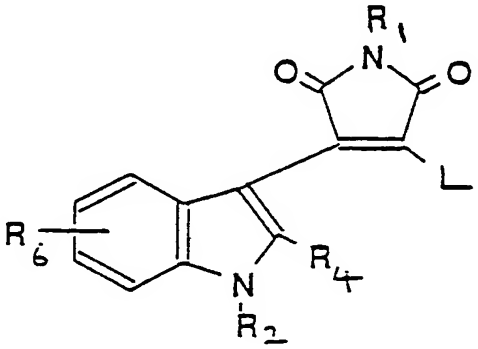


(XIX)

wherein L is a leaving group such as halogen, in a suitable solvent for example tetrahydrofuran, 1,4-dioxane, diethyl ether, benzene, toluene, or combinations thereof at 25^0-140^oC (preferably 50^o-100^oC) over 30 mins. up to 4 days (preferably 1-18 hours).

Compounds of formula (XVII) may be prepared by methods described in Brenner et al., Tetrahedron (1988) 44, 2887-2892.

Compounds of formula (XVI) may also be prepared by reacting compounds of formula (XX)

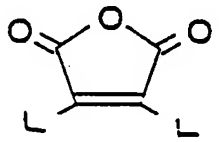


(XX)

wherein X is a leaving group such as halogen, with compounds of formula (XVII) in a suitable solvent for example tetrahydrofuran, 1,4-dioxan, benzene, toluene, diethyl ether, or combinations thereof.

Compounds of formula (XX) may be prepared by reacting compounds of formula (XIX) with compounds of formula (XVII) in a suitable solvent such as tetrahydrofuran, 1,4-dioxan, diethyl ether, benzene, toluene, or combinations thereof.

Compounds of formula (XIX) may be prepared by reacting an amine of formula R^1NH_2 with a maleic anhydride of formula (XXI)



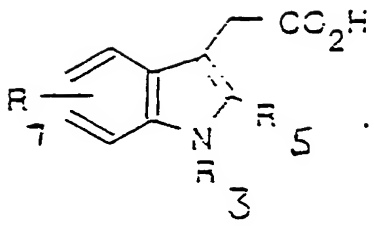
(XXI)

wherein L is a leaving group as hereinbefore defined. Compounds of formula (XXI) may be obtained commercially or prepared by methods well known in the art.

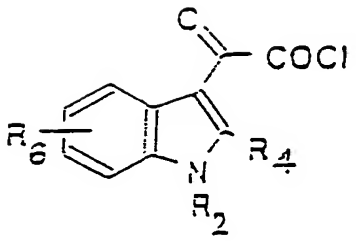
Compounds of formula (I) wherein X, Y are H, OR^{10} or H, SR^{10} may be prepared from compounds of formula (I) wherein X, Y are H, OH or H,OR^{10} or H,SR^{10}, by reaction with an alcohol R^{10}-OH or a thiol R^{10}-SH in the presence of an acid such as HCl or TFA.

Compounds of formula (I) wherein X, Y are H, OH can be prepared from compounds of formula (I) wherein R^{13} and R^{14} together form a carbonyl group by reaction with a reducing agent, for example metal hydrides such as lithium aluminium hydride, sodium cyanoborohydride.

Compounds of formula (XI) can be prepared by reacting an indole of formula (XXII) with an indole of formula (XII)



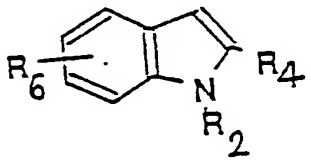
(XXII)



(XII)

in the presence of a base, such as triethylamine, ethyl diisopropylamine or pyridine and optionally a suitable solvent.

Compounds of formula (XII) may conveniently be prepared by reacting compounds of formula (XIII)



(XIII)

with oxalyl chloride, optionally in a suitable solvent, for example dichloromethane or tetrahydrofuran.

Compounds of formula (XXII) and (XIII) may be obtained commercially or prepared by methods well known to a skilled person.

Alternatively, compounds of formula (XI) may be prepared by the methods demonstrated in J.Bergman and B.Pelcman, Tetrahedron Letters (1987) 28, 4441-4444.

Compounds of formula (I) wherein the dotted line represents a double bond may be prepared by methods the same as or analogous in those described in European Patent Specification 0 397 060 and European Patent Specification 0 328 026.

It will be appreciated that when R^1, R^2 or R^3 are protecting groups, they may be introduced or removed at any stage of the process according to methods known in the art (Theodora W. Greene and Peter G.M. Wuts in Protecting Groups in Organis Syntheses (2nd Ed), 1991, Wiley and Sons). Preferred protecting groups for the indole nitrogen are tert-butyloxycarbonyl (BOC), p-toluenesulphonyl (tosyl), benzyl, benzyloxymethyl, methoxy or silyl (eg. tert-butyldimethylsily, triisopropylsilyl).

The introduction of groups R^2 and R^3 where R^2 and/or R^3 are not hydrogen may be performed at any stage of the process. For example, the indole nitrogens may be alkylated or acylated with groups R^2-L or R^3-L where R^2 and R^3 are as previously defined with the exception of hydrogen, and L is a suitable leaving group such as halogen or sulphonate ester (eg. trifluoromethanesulphonate). The reaction preferably taking place in the presence of a base (eg. triethylamine), or a metal hydride (eg. sodium hydride), or an alkyl lithium (eg. n-butyl lithium), in a suitable solvent such as dimethylformamide, tetrahydrofuran, dimethylsulphoxide.

The introduction of groups R^6 and R^7 where R^6 and/or R^7 are not hydrogen, may be performed at any stage, according to methods known in the art of indole chemistry and aromatic chemistry. For example a halogen atom may conveniently be introduced using N-halosuccinimides or by the use of a halogen. A nitro group may for example be introduced using KNO_3 or HNO_3 in the presence of sulphuric acid. Acyl (eg. formyl) or sulphonyl groups may, for example, be introduced by methods described in Chem. Ind. (1981), 338- and J.Amer.Chem.Soc (1946) 68, 1272 respectively.

Compounds of formula (I) may be converted into an ester by reaction with an appropriate esterifying agent, for example, an acid halide or anhydride. Where it is desired to isolate a compound of formula (I) as an acid addition salt, for example a physiologically acceptable acid addition salt, the salt may be formed by reacting the compound of

formula (I) in the form of the free base with the appropriate acid. The two reactants are preferably used in equivalent amounts and the reaction may be carried out in a suitable solvent such as an alcohol, for example ethanol, an ester, for example ethyl acetate, or an ether, for example tetrahydrofuran. One salt of a compound of formula (I) may be converted into another salt using standard methods, for example where it is desired to convert a salt of a compound of formula (I) with an acid which is not physiologically acceptable into a salt with a physiologically acceptable acid. An ester or salt may be converted into the parent compound, for example, by hydrolysis.

The following Examples are intended for illustration only and are not intended to limit the scope of the invention in any way. The term "active ingredient" as used in the Examples means a compound of formula (I) or a salt, ester or physiologically functional derivative of a compound of formula (I) or a solvate of any thereof.

Experimentals

General Method for the Preparation of N-Substituted-3,4-dichloro-maleimides described in Examples 1-5 below

To a solution of dichloromaleic anhydride (20g, 0.12mol) in acetic acid (60ml) was added the amine (0.12mol, 1.0 equivalent, commercially available) dropwise with stirring and cooling (ice/water bath). The mixture was then heated under reflux for 30-480 mins. (preferably 90-180 mins.). After cooling, water (100ml) was added and the resulting precipitate filtered off and purified by recrystallisation or sublimination. If the imide did not precipitate, EtOAc was added and the organic layer separated, dried (Na_2SO_4) and evaporated. The residue was redissolved in EtOAc, washed with aqueous sodium bicarbonate solution, separated, dried (Na_2SO_4) and evaporated. The residue was purified by crystallisation, sublimation, or flash chromatography over silica.

The following compounds were thus prepared.

Example 1

3,4-Dichloro-2,5-dihydro-1-(3-trifluoromethylphenylmethyl)-1H-pyrrolo-2,5-dione (1)
M.p. 82.5-83.5°C
Anal. $C_{12}H_6Cl_2F_3NO_2$ requires C, 44.47%, H, 1.87%, N, 4.32%
C, 44.36%, H, 1.82%, N, 4.44%

Example 2

3,4-Dichloro-2,5-dihydro-1-(2-pyridylmethyl)-1H-pyrrolo-2,5-dione (2)
M.p. 55-56°C

Example 3

3,4-Dichloro-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione (3)
M.p. 82-83°C
Anal. $C_5H_3Cl_2NO_2$ requires C, 33.36%, H, 1.68%, N, 7.78%
Found C, 33.04%, H, 1.65%, N, 7.62%

Example 4

3,4-Dichloro-2,5-dihydro-1-(cyclohexylmethyl)-1H-pyrrolo-2,5-dione (4)
M.p. 80-82°C
Anal. $C_{11}H_{13}Cl_2NO_2.0.1\ H_2O$ requires C, 50.04%, H, 5.00%, N, 5.31%
Found C, 49.90%, H, 5.08%, N, 5.35%

Example 5

3,4-Dichloro-2,5-dihydro-1-(4-dimethylaminophenylmethyl)-1H-pyrrolo-2,5-dione (5)
M.p. 152-154°C

Anal. $C_{13}H_{12}Cl_2N_2O_2$ requires C, 52.17%, H, 4.01%, N, 9.36%
Found C, 52.02%, H, 4.02%, N, 9.27%

Example 6

3,4-Dibromo-2,5-dihydro-1-(benzyloxymethyl)-1H-pyrrolo-2,5-dione (6)

To a solution of 2,3-dibromomaleimide (2.0g, 7.85mmol) in dry acetone (80ml) was added potassium carbonate (3.25g) at 0°C, followed by benzyloxymethyl chloride (1.2ml). The mixture was then stirred at room temperature overnight. Water (100ml) and ethyl acetate (150ml) were then added, the organic phase separated, dried (Na_2SO_4), evaporated and chromatographed over flash silica (hexane/ethyl acetate, 6:1). Evaporation of the appropriate fractions gave the title compound (6).

Anal. $C_{12}H_9Br_2NO_3.0.2H_2O$ requires C, 38.07%, H, 2.50%, N, 3.70%
Found C, 38.05%, H, 2.39%, N, 3.57%

General Method for the Preparation of 3-Chloro-2,5-dihydro-4-(1H-indol-3-yl)-1H-pyrrole-2,5-diones and 2,5-Dihydro-3,4-bis-(1H-indol-3-yl)-1H-pyrrole-2,5-diones described in Examples 7-17 below

To a solution of ethyl magnesium bromide (57mmol) in THF (25ml) under nitrogen was added a solution of the indole (57mmol) in benzene (35ml) over 40 mins. at 0°C with stirring. The solution was then stirred for a further 5-60 mins. or optionally heated at 50°C for 10-200 mins. The 3,4-dichloromaleimide derivative (14mmol) in benzene or benzene/THF (35ml) was then added dropwise over 20-60 mins. at room temperature with stirring. The solution was then heated under reflux for 30 mins. to 4 days (usually 60-480 mins.). After cooling, the mixture was quenched with 20% w/v citric acid solution or ammonium chloride solution. Ethyl acetate was added, the organic layer

separated, washed with water, dried (Na_2SO_4) and evaporated. The residue was then flash chromatographed over silica, eluting with a suitable solvent system (eg. ether/hexane, ethyl acetate/hexane, dichloromethane). The first coloured compound to be eluted was the 3-chloro-2,5-dihydro-4-(1H-indol-3-yl)-1H-pyrrole-2,5-dione, followed by the 3,4-bis-(1H-indol-3-yl)-2,5-dihydro-1H-pyrrole-2,5-dione.

The following examples were thus prepared.

Example 7

3,4-Bis(1H-indol-3-yl)-2,5-dihydro-1-(3-trifluorophenylmethyl)-1H-pyrrolo-2,5-dione (7)
M.p. 233-234°C
Anal. $C_{28}H_{11}F_3N_3O_2$ requires C, 69.28%, H, 3.74%, N, 8.60%
Found C, 69.40%, H, 3.80%, N, 8.56%

Example 8

3,4-Bis(1H-2-methylindol-3-yl)-2,5-dihydro-1-phenylmethyl-1H-pyrrolo-2,5-dione (8)
M.p. 279-280°C
Anal. $C_{29}H_{23}N_3O_2.0.14\ H_2O$ requires C, 77.74%, H, 5.24%, N, 9.38%
Found C, 77.47%, H, 4.95%, N, 9.10%

Example 9

3,4-Bis-(1H-indol-3-yl)-2,5-dihydro-1-(cyclohexylmethyl)-1H-pyrrolo-2,5-dione (9)
M.p. 240-242°C
Anal. $C_{27}H_{25}N_3O_2.0.33H_2O$ requires C, 75.54%, H, 5.98%, N, 9.79%
Found C, 75.70%, H, 6.03%, N, 9.46%

Example 10

3,4-Bis-(1H-indol-3-yl)-2,5-dihydro-1-(2-pyridylmethyl)-1H-pyrrolo-2,5-dione hydrochloride (10)

The hydrochloride salt was prepared by dissolving the parent compound in THF, on addition of chloroform previously saturated with hydrogen chloride gas, the salt precipitated and was isolated by filtration.
M.p. decomposes above 100°C

Example 11

3,4-Bis-(1H-indol-3-yl)-2,5-dihydro-1-(4-dimethylaminophenylmethyl)-1H-pyrrolo-2,5-dione (11)
M.p. 230-232°C
Anal. $C_{29}H_{24}N_4O_2$ requires C, 75.65%, H, 5.22%, N, 12.17%
Found C, 75.71%, H, 5.28%, N, 12.16%

Example 12

3,4-Bis-(7-methyl-1H-indol-3-yl)-2,5-dihydro-1-(methyl)-1H-pyrrolo-2,5-dione (12)
M.p. >320°C
Anal. $C_{23}H_{19}H_3O_2.0.2CH_3CO_2C_2H_5$ requires C, 73.86%, H, 5.36%, N, 10.86%
Found C, 73.96%, H, 5.22%, N, 11.00%

Example 13

3,4-Bis-(1H-indol-3-yl)-2,5-dihydro-1-(benzyloxymethyl)-1H-pyrrolo-2,5-dione (13)
Prepared from Example 6.
M.p. 219-221°C
Anal. $C_{28}H_{21}N_3O_3$ requires C, 75.15%, H, 4.73%, N, 9.39%
Found C, 74.88%, H, 4.64%, N, 9.24%

Example 14

3,4-Bis-(5-methoxy-1H-indol-3-yl)-2,5-dihydro-1-(3-trifluoromethyl-phenyl methyl)-1H-pyrrolo-2,5-dione (14)

M.p. 96-97°C

Anal. $C_{30}H_{22}F_3N_3O_4.0.30CH_3CO_2C_2H_5.0.70H_2O$

requires C, 64.11%, H, 4.45%, N, 7.19%

Found C, 64.17%, H, 4.18%, N, 6.91%

Example 15

3,4-Bis-(6-fluoro-1H-indol-3-yl)-2,5-dihydro-1-(methyl)-1H-pyrrolo-2,5-dione (15)

M.p. 274-276°C

Anal. $C_{21}H_{13}F_2N_3O_2.0.13CH_3CO_2C_2H_5$

requires C, 66.48%, H, 3.64%, N, 10.81%

Found C, 66.35%, H, 3.53%, N, 10.78%

Example 16

3,4-Bis-(4-fluoro-1H-indol-3-yl)-2,5-dihydro-1-(methyl)-1H-pyrrolo-2,5-dione (16)

M.p. >300°C

Anal. $C_{21}H_{13}F_2N_3O_2.0.2H_2O$ requires C, 66.22%, H, 3.55%, N, 11.03%

Found C, 66.13%, H, 3.47%, N, 10.80%

Example 17

3,4-Bis-(1H-indol-3-yl)-2,5-dihydro-1-(methyl)-1H-pyrrolo-2,5-dione (17)

M.p. 272-277°C

Reference: J. Med. Chem. (1922) 35, 177-184

General Method for the Preparation of 3,4-Bis (1H-indol 3-yl) maleic anhydrides

A solution of the 3,4-Bis(1-H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione in 10% aqueous potassium hydroxide and a co-solvent, preferably dioxan or methanol, was heated under reflux for 1-30 hours. When monitoring by tlc (SiO_2) revealed the absence of starting material, the mixture was cooled and acidified. If the product precipitated at this stage, it could be isolated by filtration and optionally crystallised. Alternatively, the product could be extracted, for example with ethyl acetate, and then purified by crystallisation or column chromatography over silica.

The following examples (18 to 20) were thus prepared.

Example 18

3,4-Bis-(1H-indol-3-yl)-maleic anhydride (18)
M.p. 125-129°C.
Anal. $C_{20}H_{12}N_2O_3.0.75H_2O$ requires C, 70.27%, H, 3.98%, N, 8.22%
Found C, 70.43%, H, 4.17%, N, 8.20%

Example 19

3,4-Bis-(7-methyl-1H-indol-3-yl)-maleic anhydride (19)
M.p. 310°C
Anal. $C_{22}H_{16}N_2O_3.0.2CH_3CO_2C_2H_5.0.3H_2O$
requires C, 72.18%, H, 4.84%, N, 7.38%
Found C, 72.08%, H, 4.71%, N, 7.21%

Example 20

3,4-Bis-(4-fluoro-1H-indol-3-yl)-maleic anhydride (20)
M.p. 161-162°C
Anal. $C_{20}H_{10}F_2N_2O_3.H_2O$ requires C, 62.74%, H, 3.18%, N, 7.32%

Found C, 62.95%, H, 3.24%, N, 7.08%

General Method for the Preparation of 1-Unsubstituted-3,4-bis-(1H-indol-3-yl)2,5-dihydro-1H-pyrrolo-2,5-diones from 3,4-bis-(1H-indol-3-yl) maleic anhydrides

A mixture of the 3,4-bis (1H-indol-3-yl)-maleic anhydride and an excess of ammonium acetate (typically 10-250 equivalents) were heated at 140° until reaction was complete (typically 15-240 mins). The mixture was then cooled, partitioned between ethyl acetate and water (brine, aqueous HCl or bicarbonate solution may be used), and the organic phase separated. After further washings, the organic phase is dried ($MgSO_4$) and evaporated. The product may then be recrystallised or purified by flash chromatography over silica. The following examples (20 and 21) were thus prepared.

Example 21

3,4-Bis (7-methyl-1H-indol-3-yl)2,5-dihydro-1H pyrrolo-2,5-dione (21)
M.p. >300°C
Anal. $C_{22}H_{17}N_3O_2.0.1CH_3CO_2C_2H_5$ requires C, 73.87%, H, 4.93%, 11.54%
Found C, 73.94%, H, 5.01%, N, 11.42%

Example 22

3,4-Bis (4-fluoro-1H-indol-3-yl)2,5-dihydro-1H-pyrrolo-2,5-dione (22)
M.p. 300-302°C
Anal. $C_{20}H_{11}F_2N_3O_2.0.26H_2O$ requires C, 65.28%, H, 3.16%, N, 11.42%
Found C, 65.20%, H, 3.08%, N, 11.44%

General Method for the Preparation of 1-Substituted-2,5-dihydro-3,4-bis (1H-indol-3-yl)-1H-pyrrolo-2,5-diones from 3,4-bis (1H-indol-3-yl) maleic anhydrides

A solution of the 3,4-bis-(1H-indol-yl) maleic anhydride in a suitable solvent, such as acetic acid, tetrahydrofuran, toluene, dimethylformamide (or combinations thereof), in combination with excess of the amine (2-10 equivs) or an excess of the amine salt and an appropriate base (e.g. ethyldiisopropylamine, potassium carbonate), was heated at 70-150°C until tlc revealed that most of the anhydride had been consumed. The solvent was then optionally evaporated in vacuo, the residue partitioned between an organic solvent (e.g. ethyl acetate) and aqueous acid (e.g. HCl, acetic acid) or aqueous base (e.g. sodium bicarbonate solution), the organic layer separated, dried ($MgSO_4$) and evaporated. Alternatively, the reaction mixture may optionally be partitioned directly by the addition of aqueous acid or base, the organic layer separated, dried ($MgSO_4$) and evaporated. The product may then be purified by crystallisation or flash chromatography over silica.

The following examples (23-24) were thus prepared.

Example 23

3-[(1-(3-Hydroxypropyl)-1H-indol-3-yl)]-4-(1H-indol-3-yl)-2,5-dihydro-1-(3-trifluoromethylphenylmethyl)-1H-pyrrolo-2,5-dione (23)

Prepared from example 26. The product was purified by flash chromatography over silica (hexane/ethyl acetate, (1:1)), and triturated with carbon tetrachloride, affording the product (23) as a dark red foam.

M.p. 95°C

Anal. $C_{31}H_{24}F_3N_3O_3 \cdot 0.2\ CCl_4$ requires C, 65.25%, H, 4.18%, N, 7.32%

Found C, 65.17%, H, 4.22%, N, 7.26%

Example 24

3-[(1-(3-Acetoxypropyl)-1H-indol-3-yl)]-4-(1H-indol-3-yl)-2,5-dihydro-1-(3-trifluoromethylphenylmethyl)-1H-pyrrolo-2,5-dione (24)

Prepared from example 26. The reaction mixture was acidified with acetic acid, then, when acetylation was complete (tlc), the mixture partitioned using ethyl acetate and water, and the organic layer separated. After washing with water, drying ($MgSO_4$) and evaporation, the product (24) was purified using flash chromatography over silica (hexane/ethyl acetate, (2:1)).

M.p. 80°C

Anal. $C_{33}H_{26}F_3N_3O_4.0.25H_2O$ requires C, 67.18%, H, 4.50%, N, 7.12%

Found C, 67.39%, H, 4.45%, N, 6.83%

Preparation of 3,4-Bis[(1-(3-hydroxypropyl)-1H-indol-3-yl)] maleic anhydride (25) and 3-[(1-[3-Hydroxypropyl)-1H-indol-3-yl)]-4-(1H-indol-3-yl) maleic anhydride (26)

To a solution of 17 (5.11g, 15mmol) in dry DMF (45ml) at 0°C under nitrogen was added sodium hydride (60% dispersion in mineral oil, 660mg, 165mmol) and the mixture stirred at room temperature for 30 minutes. The mixture was cooled to -10°C, and 3-chloropropyl acetate (2.05g, 15mmol) added. The mixture was stirred at room temperature overnight, then evaporated to dryness and taken up in ethyl acetate. After washing with brine, and drying, ($MgSO_4$), the solvent was evaporated and the residue chromatographed over flash silica (hexane/ethyl acetate, (1:1)). The coloured fractions were pooled, evaporated and dissolved in a mixture of 10% KOH solution (40ml) and dioxane (20ml). The mixture was heated under reflux for 15 hours, cooled, and acidified with concentrated hydrochloric acid. The mixture was then extracted three times with ethyl acetate, washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography over silica, eluting with hexane/ethyl acetate (1:3), gave 26 as the first eluted product.

M.P. 100°C (dec).

Anal. $C_{23}H_{18}N_2O_4.0.66H_2O$ requires C, 69.37%, H, 4.86%, N, 7.04%
Found C, 69.20%, H, 4.65%, N, 6.85%

The second eluted product was 25.

M.p. 128-130°C

Anal. $C_{26}H_{24}N_2O_5.1H_2O$ requires C, 67.53%, H, 5.63%, N, 6.06%
Found C, 67.59%, H, 5.47%, N, 5.97%

Example 27

Preparation of 3-[(1-(3-Methoxypropyl)-1H-indol-3-yl)-14-(1H-indol-3-yl)-1-(3-trifluoromethylphenylmethyl)-1H-pyrrolo-2,5-dione (27)

To a solution of trifluoromethane sulphonic anhydride (52µl, 0.31mmol) in dry dichloromethane (10ml) at 0°C under nitrogen was added a mixture of 23 (114mg, 0.21mmol) and 2,6 lutidine (4.9µl, 0.42mmol) in dry dichloromethane (7ml) with stirring. The mixture was stirred at room temperature overnight, evaporated to dryness, and the residue dissolved in methanol (15ml) at 0°C. Sodium methoxide (35mg) in methanol (2ml) was added, and the mixture stirred overnight at room temperature. The mixture was then evaporated to dryness and purified by flash chromatography over silica, eluting with CH_2Cl_2/EtOAc (19:1), then (4:1). This afforded the product (27) as a dark red solid.

M.p. 80-85°C

Anal. $C_{32}H_{26}F_3N_3O_3$ requires C, 68.94%, H, 4.67%, N, 7.54%
Found C, 68.72%, H, 4.78%, N, 7.49%

Example 28

Preparation of cis-3,4-Bis(2-methyl-1H-indol-3-yl)-1-phenylmethyl-succinimide (28)

To a solution of 8 (250mg, 0.56mmol) in ethanol (30ml) containing HCl (6N, 1.5ml) was added zinc amalgam and the mixture heated under reflux for 35 minutes. After cooling, water (20ml) and ethyl acetate (40ml) were added, and the mixture filtered through a cotton wool plug. Saturated NH_4Cl solution (5ml) was added, the organic layer separated and washed with 10% $NaHCO_3$ solution. After drying (Na_2SO_4), the organic phase was evaporated and chromatographed over flash silica, eluting with hexane/ethyl acetate (1:1). The product (28) crystallised from the column fractions as a white solid.

M.p. 214-215°C

Anal. $C_{29}H_{25}N_3O_2.H_2O$ requires C, 74.82%, H, 5.85%, N, 9.03%

Found C, 74.69%, H, 5.62%, N, 8.68%

Preparation of 3,4-Bis(1-cyclohexylmethyl-1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione (29) and 3-(1-Cyclohexylmethyl-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione (30)

To a solution of 17 (3.41g, 10mmol) in dry DMF (30ml) at 0.°C under nitrogen was added sodium hydride (440mg, 11mmol, 60% dispersion in mineral oil). The mixture was stirred at room temperature for 30 minutes, cooled to -10°C, cyclohexylmethylbromide (1.77g, 10mmol) added and the mixture stirred at room temperature for 20 hours. The mixture was then evaporated to dryness, taken up in ethyl acetate, washed with brine, dried (Na_2SO_4) and evaporated. Chromatography of the residue over flash Silica, eluting with hexane/ethyl acetate (5:2) gave 29 as the first red product to be eluted.

M.p. 238-241°C

Anal. $C_{35}H_{39}N_3O_2.0.1CH_3CO_2C_2H_5$ requires C, 78.41%, H, 7.35%, N, 7.75%

Found C, 78.32%, H, 7.57%, N, 7.62%

The second red compound eluted was 30.

M.p. 198-201°C

Anal. $C_{28}H_{27}H_3O_2.0.25H_2O$ requires C, 76.10%, H, 6.23%, N, 9.51%

Found C, 76.19%, H, 6.35%, N, 9.32%

Preparation of 3,4-Bis(1-(3-phenoxyphenylmethyl)-1H-indol-3-yl)1-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione (31) and 3-(1H-Indol-3-yl)-4-[1-(3-phenoxy)phenyl methyl-1H-indol-3-yl]-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione (32)

These compounds were prepared in the same manner as examples 28 and 29, replacing cyclohexylmethylbromide with 3-phenoxybenzylchloride, and using a reaction time of 70 hours.

The first coloured compound eluted was collected and triturated with carbon tetrachloride to give 31 as an orange semi-solid.

M.p. froths at 83°C

Anal. $C_{47}H_{35}N_3O_4.0.3CCl_4$ requires C, 75.56%, H, 4.66%, N, 5.59%

Found C, 75.75%, H, 4.63%, N, 5.54%

The second coloured compound eluted was collected and triturated with carbon tetrachloride to give 32 as a red semi-solid.

M.p. froths at 100°C

Anal. $C_{34}H_{25}N_3O_3.0.4CCl_4$ requires C, 70.61%, H, 4.28%, N, 7.18%

Found C, 70.72%, H, 4.32%, N, 7.08%

Examples

The following examples illustrate pharmaceutical formulations according to the invention to which the active ingredient is a pharmaceutically acceptable compound according to the invention.

Example 33

Tablet Formulations

The following formulations A, B and C are prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of the magnesium stearate and compression.

Formulation A

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose B.P.	210	26
(c)	Povidone B.P.	15	9
(d)	Sodium Starch Glycollate	20	12
(e)	Magnesium Stearate	5	3
		500	300

Formulation B

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose	150	-
(c)	Avicel PH 101	60	26
(d)	Povidone B.P.	15	9
(e)	Sodium Starch Glycollate	20	12
(f)	Magnesium Stearate	5	3
		500	300

Formulation C

	mg/tablet
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium stearate	4
	359

The following formulations, D and E, are prepared by direct compression of the admixed ingredients.

Formulation D

	mg/capsule
Active Ingredient	250
Pregelatinised Starch NF15	150
	400

Formulation E

	mg/capsule
Active Ingredient	250
Lactose	150
Avicel	100
	500

Formulation F (Controlled Release Formulation)

The formulation is prepared by wet granulation of the following ingredients with a solution of povidone followed by addition of the magnesium stearate and compression.

		mg/tablet
(a)	Active Ingredient	500
(b)	Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c)	Lactose B.P.	53
(d)	Povidone B.P.C.	28
(e)	Magnesium Stearate	7
		700

Drug release takes place over a period of about 6-8 hours and is complete after 12 hours.

Example 34

Capsule Formulations

Formulation A

A capsule formulation is prepared by admixing the ingredients of Formulation D in Example 3 above and filling into two-part hard gelatin capsule.

Formulation B

		mg/capsule
(a)	Active ingredient	250
(b)	Lactose B.P.	143
(c)	Sodium Starch Glycollate	25
(d)	Magnesium Stearate	2
		420

Capsules are prepared by admixing the above ingredients and filling into two-part hard gelatin capsules.

Formulation C

	mg/capsule
(a) Active ingredient	250
(b) Macrogol 4000 BP	350
	600

Capsules are prepared by melting the Macrogol 4000 BP, dispersing the active ingredient in the melt and filling the melt into two-part hard gelatin capsules.

Formulation D

	mg/capsule
Active ingredient	250
Lecithin	100
Arachis Oil	100
	450

Capsules are prepared by dispersing the active ingredient in the lecithin and arachis oil and filling the dispersion into soft, elastic gelatin capsules.

Formulation E (Controlled Release Capsule)

The following controlled release capsule formulation is prepared by extruding ingredients (a), (b) and (c) using an extruder, followed by spheronisation of the extrudate and drying. The dried pellets are then coated with the release-controlling membrane (d) and filled into two-piece, hard gelatin capsules.

		mg/capsule
(a)	Active Ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose BP	125
(d)	Ethyl Cellulose	13
		513

Example 35

Injectable Formulation

Formulation A

Active ingredient	0.200g
Hydrochloric acid solution, 0.1M	q.s. to pH 4.0 to 7.0
Sodium hydroxide solution, 0.1M	q.s. to pH 4.0 to 7.0
Sterile water	q.s. to 10ml

The active ingredient is dissolved in most of the water (35°-40°C) and the pH adjusted to between 4.0 and 7.0 using the hydrochloric acid or the sodium hydroxide as appropriate. The batch is then made up to volume with the water and filtered through a sterile micropore filter into a sterile amber glass vial 10ml and sealed with sterile closures and overseals.

Formulation B

Active ingredient	0.125 g
Sterile, pyrogen-free, pH 7 phosphate buffer,	q.s. to 25 ml

Example 36

Intramuscular injection

Active Ingredient		0.20 g
Benzyl Alcohol		0.10 g
Glycofurol 75		1.45 g
Water for Injection	q.s. to	3.00 ml

The active ingredient is dissolved in the glycofurol. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile amber glass vials 3 ml.

Example 37

Syrup

Active ingredient		0.25 g
Sorbitol Solution		0.10 g
Glycerol		2.00 g
Sodium Benzoate		0.005 g
Flavour, Peach 17.42.3169		0.0125 ml
Purified Water	q.s. to	5.00 ml

The active ingredient is dissolved in a mixture of the glycerol and most of the purified water. An aqueous solution of the sodium benzoate is then added to the solution, followed by addition of the sorbitol solution and finally the flavour. The volume is made up with purified water and mixed well.

Example 38

Suppository

	mg/suppository
Active Ingredient	250
Hard Fat, BP (Witepsol H15 - Dynamit Nobel)	1770
	2020

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200 μm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension and stirred to ensure a homogenous mix. The entire suspension is passed through a 250 μm stainless steel screen and, with continuous stirring, is allowed to cool to 40°C. At a temperature of 38°C to 40°C, 2.0g of the mixture is filled into suitable, 2 ml plastic moulds. The suppositories are allowed to cool to room temperature.

Example 39

Pessaries

	mg/pessary
Active ingredient	250
Anhydrate Dextrose	380
Potato Starch	363
Magnesium Stearate	7
	1000

The above ingredients are mixed directly and pessaries prepared by direct compression of the resulting mixture.

Example 40

Antiviral Testing

(a) HeLa-CD4$^+$ cell assay for evaluating susceptibility of HIV to antiviral compounds

Susceptibility of HIV to inhibitors was determined by infection of HT4-6C cell monolayers as described by Larder, B.A., Chesebro, B. & Richman, D.D. Antimicrob. Agents Chemother. 1990 34, 436-441. Briefly cells were seeded in 24-well multiwells at $5x10^4$ cells per well and incubated overnight at 37°C in growth medium (DMEM10). Monolayers were infected with 100-200pfu of cell-free virus in 0.2ml of DMEM containing 5% fetal bovine serum plus antibiotics (DMEM5) and incubated for 1 hour at 37°C to allow virus adsorption. Following this time, 0.8ml of DMEM5 (with or without inhibitor) was added to each well and cultures were incubated at 37°C for 2-3 days. Monolayers were fixed with 10% formaldehyde solution in PBS and stained with 0.25% crystal violet in order to visualize virus plaques. Individual foci of multinucleated gian cells (plaques) were apparent using this staining procedure. ID_{50} values were derived from plots of percent plaque reduction versus inhibitor concentration.

(b) HSV Assay

Herpes Simplex Virus types 1 (HSV 1) and 2 (HSV 2) were assayed in monolayers of Vero cells in multiwell trays. The virus strains used were SC16 and 186 for HSV-1 and HSV-2 respectively. Activity of compounds was determined in the plaque reduction assay, in which a cell monolayer was infected with a suspension of the appropriate HSV, and then overlaid with nutrient carboxymethyl cellulose in the form of a gel to ensure that there was no spread of virus throughout the culture. A range of concentrations of compound of known molarity was incorporated in

the nutrient carboxymethyl cellulose overlay. Plaque numbers at each concentration is expressed as percentages of the control and a dose-response curve was drawn.

(c) CMV Assay

Human cytomogalovirus (HCMV) was assayed in monolayers of either MRC5 cells (human embryonic lung) in multiwell trays. The standard CMV strain AD 169 was used. Activity of compounds is determined in the plaque reduction assay, in which a cell monolayer is infected with a suspension of HCMV, and then overlaid with nutrient carboxymethyl cellulose in the form of a gel to ensure that there is no spread of virus throughout the culture. A range of concentrations of compound of known molarity was incorporated in the nutrient agarose overlay. Plaque numbers at each concentration of drug are expressed as percentage of the control and a dose-response curve is drawn.

	CMV $IC_{50}\mu M$	Cytotoxicity $CCID_{50}\mu M$
3,4-Bis-(1H-indol-3-yl)-2,5-dihydro-1-(4-dimethylamino-phenylmethyl)-1H-pyrrolo-2,5-dione	4	>500
Cis-3,4-bis(2-methyl-1H-indol-3-yl)-1-phenylmethylsuccinimide	8.5	272

(d) VZV Assay

Clinical isolates of varicella zoster virus (VZV) were assayed in monolayers of MRC-5 cells. MRC-5 cells are derived from human

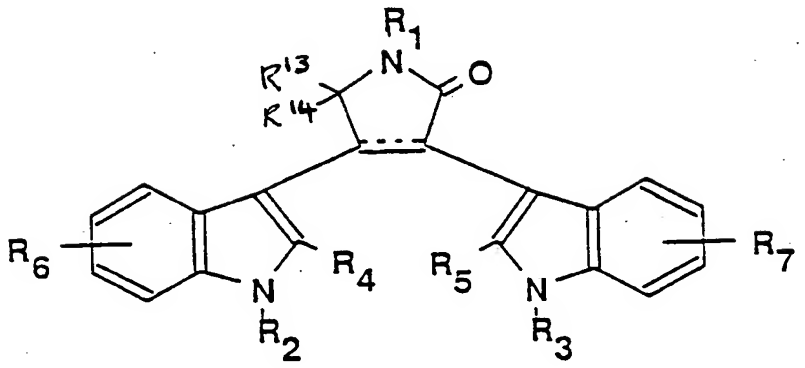
embryonic lung tissue. A plaque reduction assay was used in which a suspension of the virus stock was used to infect monolayers of the cells in multiwell trays. A range of concentrations of the compound under test of known molarity was added to the wells. Plaque numbers at each concentration were expressed as percentages of the control and a dose response curve was contructed. From these curves the 50% inhibitory concentration of each drug was determined.

(e) Cell Toxicity

Cell toxicity is assessed in cell growth inhibition assay. Subconfluent cultures of Vero cells grown on 96-well microtiter dishes are exposed to different dilutions of drug, and cell viability determined daily on replicate cultures using uptake of a tetrazolium dye (MTT). The concentration required for 50% inhibition of cell viability at 96 hours is termed $CCID_{50}$.

CLAIMS

1. Use of a compound of formula (I)



(I)

wherein
the dotted line represents an optional bond;

R^1 represents:

-H;

$-COR^{10}$, $-COOR^{10}$ where R^{10} is C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylalkyl, C_{1-6}alkenyl, or H;

$-OR^{10}$ wherein R^{10} is as hereinbefore defined;

$-C_{1-8}$alkyl, C_{1-8}alkenyl or C_{3-8}cycloalkyl where the alkyl, alkenyl or cycloalkyl moiety may be optionally substituted by one or more substituents selected from halogen, cyano, nitro, azido, $-OR^{10}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-NR^{11}R^{12}$ (where R^{11} and R^{12}, which may be the same or different, each represent H, $-COR^{10}$ where R^{10} is as hereinbefore defined, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylalkyl, tetrahydronaphthyl or indanyl or $-R^{11}R^{12}$ together with the N atom to which they are attached form a 3-,4-,5- or 6-

membered heterocyclic ring in which from 1 to 3 of the carbon atoms may be replaced by heteroatoms independently selected from O, N and S, which ring being

where possible, partially or completely unsaturated), -T-C(=Z)-W (where T is NH or S, Z is NH, S or O and W is $NR^{11}R^{12}$ where R^{11} and R^{12} are each as defined above), non-aromatic heterocycle, -NH-non-aromatic-heterocycle and aryl, such heterocycle or aryl groups being optionally substituted by one or more substituents selected from $-OR^{10}$, $-NR^{11}R^{12}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-CO_2R^{10}$, nitro, cyano, SCN, C_{1-6}alkyl (wherein one or more hydrogen atoms are optionally replaced by a halogen atom), C_{3-6}cyaloalkyl hydroxyC_{1-6}alkyl, $CONH_2$, halogen and methylenedioxy, where $R^{10}R^{11}$ and R^{12} are each as defined above;

$-NR^{11}R^{12}$ where R^{11} and R^{12} are each as defined above;

-aryl optionally substituted by one or more substituent(s) selected from $-OR^{10}$, $-NR^{11}R^{12}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-CO_2R^{10}$, nitro, cyano, SCN, C_{1-6}alkyl (wherein one or more hydrogen atoms are optionally replaced by a halogen atom), C_{3-6}cycloalkyl, hydroxyC_{1-6}alkyl, $CONH_2$, halogen and methylenedioxy, where R^{10}, R^{11} and R^{12} are each a defined above;

- a cyclic group containing from 3 to 6 carbon atoms in which from 1 to 3 of said atoms may be replaced by heteratom(s) independently selected from O, S and N;

-NH-cyclic group containing from 3 to 6 carbon atoms in which from 1 to 3 of said atoms may be replaced by heteratom(s) independently selected from O, S and N.

R^2 and R^3, which may be the same or different, are each independently selected from:-

H;

$-COR^{10}$, $-COOR^{10}$ where R^{10} is a C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylalkyl, C_{1-6}alkenyl, or H;

$-OR^{10}$ wherein R^{10} is as hereinbefore defined;

$-C_{1-8}$alkyl, C_{1-8}alkenyl or C_{3-8}cycloalkyl where the alkyl, alkenyl or cycloalkyl moiety may be optionally substituted by one or more substituents selected from halogen, cyano, nitro, azido, C_{3-8}cycloalkyl $-OR^{10}$, $-CO_2R^{10}$, $-OCOR^{10}$, $-SR^{10}$, $-SOR^{10}$, SO_2R^{10}, $-CO_2NR^{11}R^{12}$, $-NR^{11}R^{12}$ (where R^{11} and R^{12}, which may be the same or different, each represent H, $-COR^{10}$ where R^{10} is as hereinbefore defined, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylalkyl, tetrahydronaphthyl or indanyl or $-R^{11}R^{12}$ together with the N atom to which they are attached form a 3-,4-,5- or 6- membered heterocyclic ring in which from 1 to 3 of the carbon atoms may be replaced by heteroatoms independently selected from O, N and S which ring being

where possible, partially or completely unsaturated); $-T-\overset{Z}{\overset{\|}{C}}-W$ (where T is NH or S, Z is NH, S or O and W is $NR^{11}R^{12}$ where R^{11} and R^{12} are each as defined above), non-aromatic heterocycle, -NH-non-aromatic-heterocycle and aryl, such heterocycle or aryl groups being optionally substituted by one or more substituents selected from $-OR^{10}$, $-NR^{11}R^{12}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-CO_2R^{10}$, nitro, cyano, SCN, C_{1-6}alkyl (wherein one or more hydrogen atoms are optionally replaced by a halogen atom), C_{3-6} cycloalkyl, hydroxylC_{1-6}alkyl, $CONH_2$, halogen and methylene dioxy, where $R^{10}R^{11}$ and R^{12} are each as defined above);

$-NR^{11}R^{12}$ where R^{11} and R^{12} are each as defined above;

-aryl optionally substituted by one or more substituent(s) selected from $-OR^{10}$, $-NR^{11}R^{12}$, SR^{10}, $-SOR^{10}$, $-SO_2R^{10}$, CO_2R^{10},

nitro, cyano, SCN, C_{1-6}alkyl, C_{3-6}cycloalkyl, haloalkyl, hydroxyC_{1-6}alkyl, $CONH_2$, halogen and methylenedioxy, where R^{10}, R^{11} and R^{12} are each as defined above;

R^4 and R^5, which may be the same or different, are each independently selected from:

H;

-C_{1-6}alkyl or C_{3-7}cycloalkyl (where the alkyl moiety may be optionally substituted by one or more substituent(s) selected from $-OR^{10}$ $-NR^{11}R^{12}$, where R^{10}, R^{11} or R^{12} are as defined above, halogen and aryl);

-aryl optionally substituted by one or more substituent(s) selected from OH, $-OR^{10}$, $-NR^{11}R^{12}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-CO_2R^{10}$, nitro, cyano, SCN, C_{1-6}alkyl (wherein one or more hydrogen atoms are optionally replaced by a halogen atom), C_{3-6}alkyl, hydroxyC_{1-6}alkyl, $CONH_2$, halogen and methylenedioxy, where $R^{10}R^{11}$ and R^{12} are each as defined above;

R^6 and R^7, which may be the same or different, each represent one or more ring substituent(s) selected from:

H;

-C_{1-6}alkyl optionally substituted by one or more substituents independently selected from halogen, $-NR^{11}R^{12}$, cyano, $-OR^{10}$, azido, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, wherein R^{10}, R^{11} and R^{12} are as hereinbefore defined;

-cyano, nitro, halogen, methylenedioxy, $-OR^{10}$, $-SR^{10}$, $-SOR^{10}$, $-NHSO_2R^{10}$, $-SO_2R^{10}$, $-SO_2NR^{11}R^{12}$, $-CO_2R^{10}$, $-OCOR^{10}$, $-CONR^{11}R^{12}$ and $-NR^{11}R^{12}$ where R^{10}, R^{11} and R^{12} are as defined above;

R^{13} and R^{14} together form a carbonyl group (>=O) or R^{13} is X and R^{14} is Y and X and Y are both H, or one of X and Y is H and the other is $-OR^{10}$ or $-SR^{10}$, wherein R^{10} is as hereinbefore defined;

or a salt, ester or physiologically functional derivative thereof or a solvate of any thereof, for the manufacture of a medicament for the treatment or prophylaxis of at least one viral infection.

2. Use according to claim 1 wherein the viral infection is selected from herpes virus, retrovirus, hepatatis virus, coxsackie virus and hepatitis C virus infections.

3. Use according to claim 2 wherein the herpes virus infection is selected from HSV1, HSV2, VZV, CMV, EBV and HHV6.

4. Use according to claim 3 wherein the herpes virus infection is CMV.

5. Use according to any one of claims 1 to 4 wherein the compound of formula (I) is selected from:-

3,4-Bis(7-methyl-1H-indol-3-yl)2,5-dihydro-1H-pyrrolo-2,5-dione;

3,4-Bis(4-fluoro-1H-indol-3-yl)2,5-dihydro-1H-pyrrolo-2,5-dione;

3,4-Bis(5-methoxy-1H-indol-3-yl)2,5-dihydro-1-(3-trifluoromethyl phenylmethyl)-1H-pyrrolo-2,5-dione;

3,4-Bis(1H-indol-3-yl)-2,5-dihydro-1-(benzyloxymethyl)-1H-pyrrolo-2,5-dione;

3,4-Bis(6-fluoro-1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

3,4-Bis(1H-indol-3-yl)-2,5-dihydro-1-(4-dimethylamino phenylmethyl)-1H-pyrrolo-2,5-dione;

3,4-Bis(1H-indol-3-yl)-2,5-dihydro-1-(2-pyridylmethyl)-1H-pyrrolo-2,5- dione;

Cis-3,4-Bis(2-methyl-1H-indol-3-yl)-1-(phenylmethyl)-succinimide;

3-(1-Cyclohexylmethyl-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

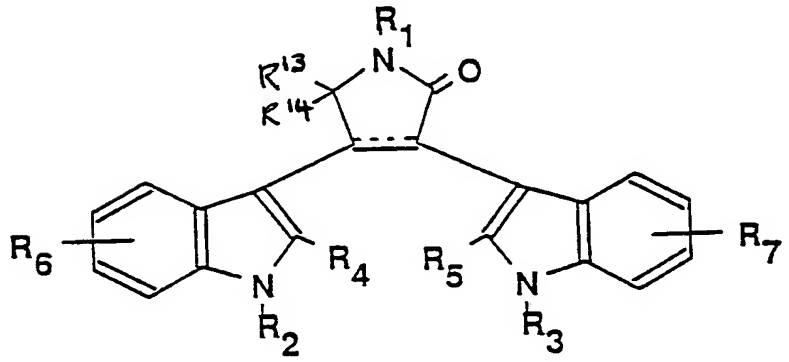
3-(1-(3-Acetoxypropyl)-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

3-(1-(3-Methoxypropyl)-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

3-(1-(3-Phenoxy phenylmethyl)-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

or a salt, ester or a physiologically functional derivative thereof or a solvate of any thereof.

6. A compound of formula (IA)



(IA)

wherein

the dotted line does not represent a bond

R^1 represents:

-H;

$-COR^{10}$, $-COOR^{10}$ where R^{10} is C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylalkyl, C_{1-6}alkenyl, or H;

$-OR^{10}$ wherein R^{10} is as hereinbefore defined;

$-C_{1-8}$alkyl, C_{1-8}alkenyl or C_{3-8}cycloalkyl where the alkyl, alkenyl or cycloalkyl moiety may be optionally substituted by one or more substituents selected from halogen, cyano, nitro, azido, $-OR^{10}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-NR^{11}R^{12}$ (where R^{11} and R^{12}, which may be the same or different, each represent H, $-COR^{10}$ where R^{10} is as hereinbefore defined, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylalkyl, tetrahydronaphthyl or indanyl or $-R^{11}R^{12}$ together with the N atom to which they are attached form a 3-,4-,5- or 6-membered heterocyclic ring in which from 1 to 3 of the carbon atoms may be replaced by heteroatoms independently selected from O, N and S, which ring being where possible, partially or completely unsaturated), $-T-\overset{Z}{\overset{\|}{C}}-W$ (where T is NH or S, Z is NH, S or O and W is $NR^{11}R^{12}$ where R^{11} and R^{12} are each as defined above), non-aromatic heterocycle, -NH-non-aromatic-heterocycle and aryl, such heterocycle or aryl groups being optionally substituted by one or more substituents selected from $-OR^{10}$, $-NR^{11}R^{12}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-CO_2R^{10}$, nitro, cyano, SCN, C_{1-6}alkyl (wherein one or more hydrogen atoms are optionally replaced by a halogen atom), C_{3-6}cycloalkyl, hydroxyC_{1-6}alkyl, $CONH_2$, halogen and methylenedioxy, where $R^{10}R^{11}$ and R^{12} are each as defined above;

$-NR^{11}R^{12}$ where R^{11} and R^{12} are each as defined above;

-aryl optionally substituted by one or more substituent(s) selected from $-R^{10}$, $-NR^{11}R^{12}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-CO_2R^{10}$, nitro, cyano, SCN, C_{1-6}alkyl (wherein one or more hydrogen atoms are optionally replaced by a halogen atom), C_{3-6}cycloalkyl, hydroxyC_{1-6}alkyl, CON_2, halogen and methylenedioxy, where R^{10}, R^{11} and R^{12} are each as defined above;

- a cyclic group containing from 3 to 6 carbon atoms in which from 1 to 3 of said atoms may be replaced by heteratom(s) independently selected from O, S and N:

-NH-cyclic group containing from 3 to 6 carbon atoms in which from 1 to 3 of said atoms may be replaced by heteratom(s) independently selected from O, S and N;

R^2 and R^3, which may be the same or different, are each independently selected from:-

H;

$-COR^{10}$, $-COOR^{10}$ where R^{10} is a C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylalkyl, C_{1-6}alkenyl, or H;

$-OR^{10}$ wherein R^{10} is as hereinbefore defined;

$-C_{1-8}$alkyl, C_{1-8}alkenyl or C_{3-8}cycloalkyl where the alkyl, alkenyl or cycloalkyl moiety may be optionally substituted by one or more substituents selected from halogen, cyano, nitro, azido, C_{3-8}cycloalkyl $-OR^{10}$, $-CO_2R^{10}$, $-OCOR^{10}$, $-SR^{10}$, $-SOR^{10}$, SO_2R^{10}, $-CO_2NR^{11}R^{12}$, $-NR^{11}R^{12}$ (where R^{11} and R^{12}, which may be the same or different, each represent H, $-COR^{10}$ where R^{10} is as hereinbefore defined, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylalkyl, tetrahydronaphthyl or indanyl or $-R^{11}R^{12}$ together with the N atom to which they are attached form a 3-,4-,5- or 6- membered heterocyclic ring in which from 1 to 3 of the carbon atoms may be

replaced by heteroatoms independently selected from O, N and S which ring being

where possible, partially or completely unsaturated); -T-C(=Z)-W (where T is NH or S, Z is NH, S or O and W is $NR^{11}R^{12}$ where R^{11} and R^{12} are each as defined above), non-aromatic, heterocycle, -NH-non-aromatic-heterocycle and aryl, such heterocycle or aryl groups being optionally substituted by one or more substituents selected from $-OR^{10}$, $-NR^{11}R^{12}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-CO_2R^{10}$, nitro, cyano, SCN, C_{1-6}alkyl (wherein one or more hydrogen atoms are optionally replaced by a halogen atom), C_{3-6} cycloalkyl, hydroxylC_{1-6}alkyl, $CONH_2$, halogen and methylenedioxy, where R^{10} R^{11} and R^{12} are each as defined above);

$-NR^{11}R^{12}$ where R^{11} and R^{12} are each as defined above;

-aryl optionally substituted by one or more substituent(s) selected from $-OR^{10}$, $-NR^{11}R^{12}$, SR^{10}, $-SOR^{10}$, $-SO_2R^{10}$, CO_2R^{10}, nitro, cyano, SCN, C_{1-6}alkyl, C_{3-6}cycloalkyl, haloalkyl, hydroxyC_{1-6}alkyl, $CONH_2$, halogen and methylenedioxy, where R^{10}, R^{11} and R^{12} are each as defined above;

R^4 and R^5, which may be the same or different, are each independently selected from:

H;

$-C_{1-6}$alkyl or C_{3-7}cycloalkyl (where the alkyl moiety may be optionally substituted by one or more substituent(s) selected from $-OR^{10}$ $-NR^{11}R^{12}$, where R^{10}, R^{11} or R^{12} are as defined above, halogen and aryl);

-aryl optionally substituted by one or more substituent(s) selected from OH, $-OR^{10}$, $-NR^{11}R^{12}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-CO_2R^{10}$, nitro, cyano, SCN, C_{1-6}alkyl wherein one or more

hydrogen atoms are optionally replaced by a halogen atom, C_{3-6}alkyl, hydroxyC_{1-6}alkyl, $CONH_2$, halogen and methylenedioxy, where $R^{10}R^{11}$ and R^{12} are each as defined above;

R^6 and R^7, which may be the same or different, each represent one or more ring substituent(s) selected from:

H;

-C_{1-6}alkyl optionally substituted by one or more substituents independently selected from halogen, $-NR^{11}R^{12}$, cyano, $-OR^{10}$, azido, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, wherein R^{10}, R^{11} and R^{12} are as hereinbefore defined.

-cyano, nitro, halogen, methylenedioxy, $-OR^{10}$, $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-SO_2NR^{11}R^{12}$, $-CO_2R^{10}$, $-OCOR^{10}$, $-CONR^{11}R^{12}$ and $-NR^{11}R^{12}$ where R^{10}, R^{11} and R^{12} are as defined above;

R^{13} and R^{14} together form a carbonyl group (>=O) or R^{13} is X and R^{14} is Y and X and Y are both H, or one of X and Y is H and the other is $-OR^{10}$ or $-SR^{10}$, wherein R^{10} is as hereinbefore defined;

or a salt, ester or physiologically functional derivative thereof or a solvate of any thereof; excluding the compounds Cis-3,4-bis-(1H-indol-3-yl)-2,5-pyrrolidinedione and trans-3,4-bis-(1H-indol-3-yl)-2,5-pyrrolidinedione.

7. A compound of formula (IA) as shown in claim 6 wherein the dotted line represents an optional bond and R^{13} is X and R^{14} is Y and one of X and Y is H and the other is $-OR^{10}$ (excluding OH) or $-SR^{10}$ wherein R^{10}.

8. A compound of formula (IA) as shown in claim 6 wherein the dotted line represents a bond, R^1 is H or C_{1-8}alkyl optionally substituted by one or more substituents selected from $-OR^{10}$,

$-OCOR^{10}$, wherein R^{10} and aryl optional substituted by one or more substituents selected from C_{1-6}alkyl wherein one or more hydrogen atoms are replaced by a halogen atom and $-NR^{11}R^{12}$ wherein R^{11} and R^{12} are as hereinbefore defined; R^2 and R^3, which may be the same, or different, are each independently selected from H and C_{1-8}alkyl substituted by one or more substituents selected from $-OR^{10}$ wherein R^{10} is as hereinbefore defined, C_{3-8}cycloalkyl and aryl optionally substituted by one or more substituents selected from C_{1-6}alkyl wherein one or more hydrogen atoms are replaced by a halogen atom and $-OR^{10}$ wherein R^{10} is as hereinbefore defined; R^4 and R^5 which may be the same or different, are each independently selected from H and C_{1-6}alkyl; R^6 and R^7, which may be the same or different, each represent one or more ring substituent(s) selected from H, C_{1-6}alkyl, $-OR^{10}$ wherein R^{10} is as hereinbefore defined and halogen and R^{13} and R^{14} together form a carbonyl group; or a salt, ester or physiologically acceptable derivative thereof or a solvate of any thereof; excluding 3,4-bis-1H-indol-3-yl-1-(phenylmethyl)-1H-pyrrole-1,5-dione.

9. A compound according to claim 8 selected from:-

3,4-Bis(7-methyl-1H-indol-3-yl)2,5-dihydro-1H-pyrrolo-2,5-dione;

3,4-Bis(4-fluoro-1H-indol-3-yl)2,5-dihydro-1H-pyrrolo-2,5-dione;

3,4-Bis(5-methoxy-1H-indol-3-yl)2,5-dihydro-1-(3-trifluoromethyl phenylmethyl)-1H-pyrrolo-2,5-dione;

3,4-Bis(1H-indol-3-yl)-2,5-dihydro-1-(benzyloxymethyl)-1H-pyrrolo-2,5-dione;

3,4-Bis(6-fluoro-1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

3,4-Bis(1H-indol-3-yl)-2,5-dihydro-1-(4-dimethylamino phenylmethyl)-1H-pyrrolo-2,5-dione;

3,4-Bis(1H-indol-3-yl)-2,5-dihydro-1-(2-pyridylmethyl)-1H-pyrrolo-2,5- dione;

Cis-3,4-Bis(2-methyl-1H-indol-3-yl)-1-(phenylmethyl)-succinimide;

3-(1-Cyclohexylmethyl-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

3-(1-(3-Acetoxypropyl)-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

3-(1-(3-Methoxypropyl)-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

3-(1-(3-Phenoxy phenylmethyl)-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione;

or a salt, ester or a physiologically functional derivative thereof or a solvate of any thereof.

10. A pharmaceutical formulation comprising a compound according to any one of claims 6 to 9, together with a pharmaceutically acceptable carrier therefore.

11. A formulation according to claim 10 in unit dosage form.

12. A formulation according to claim 11 in the form of a tablet or capsule.

13. A compound according to any one of claims 6 to 9 or a formulation according to any one of claims 10 to 12 for use in therapy.

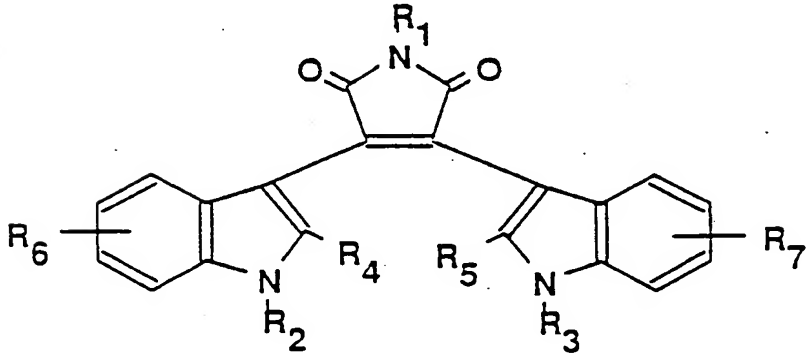
14. A compound as defined in claim 1 which compound is 3,4-bis(1H-indol-3-yl)-1-(phenylmethyl)-2,5-pyrrolidinedione for use in therapy.

15. A compound as defined in claim 1 which compound is cis-3,4-bis-(1H-indol-3-yl)-2,5-pyrrolidinedione for use in therapy.

16. A method of treatment or prevention of the symptoms or effects of a viral infection in an infected host which comprises administering to said host a therapeutically effective non-toxic amount of a compound of formula (I) as claimed in claim 1.

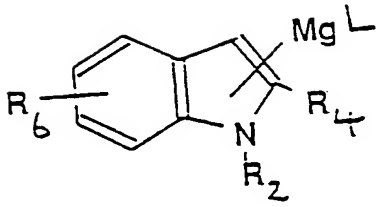
17. A process for the preparation of a compound of formula (IA) as defined in any one of claims 6 to 9 which comprises:-

(A) for the preparation of a compound wherein the dotted line does not represent a bond and R^{13} and R^{14} together form a carbonyl group, by reducing a compound of formula (XVI)

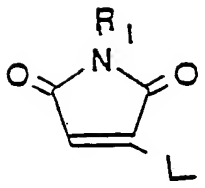


(XVI)

(B) for the preparation of a compound wherein the dotted line does not represent a double bond and R^{13} and R^{14} together form a carbonyl group by reacting a compound of formula (XVII) with a compound of formula (XVIII)

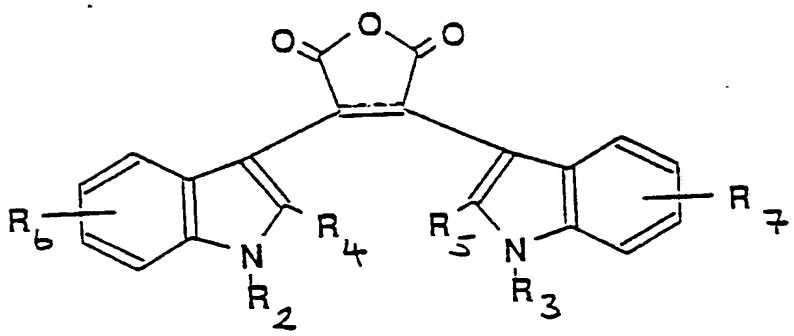


(XVII)



(XVIII)

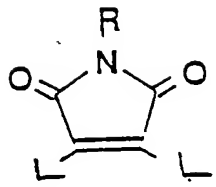
(C) for the preparation of a compound wherein R^{13} and R^{14} together form a carbonyl group, by reacting a compound of formula (XI)



(XI)

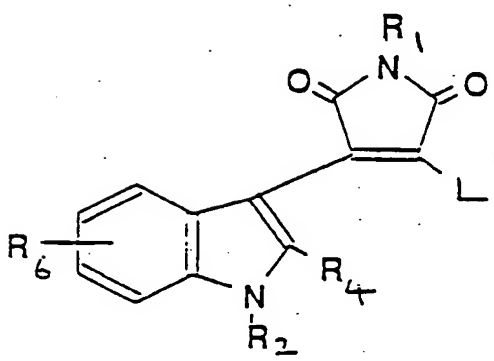
with an amine of formula R^1NH_2 or R^1NH_3X wherein X^1 represents an acid anion.

(D) for the preparation of a compound wherein the dotted line represents a double bond and R^{13} and R^{14} together form a carbonyl group, by reacting a compound of formula (XVII) as defined above with a compound of formula (XIX) or (XX)



(XIX)

or



(XX)

(E) for the preparation of a compound wherein X is H and Y is OH, by reducing a compound of formula (IA) wherein R^{13} and R^{14} together form a carbonyl group, optionally converting the compound of formula (IA) so formed to a compound of formula (IA) wherein X and Y are both H;

(F) for the preparation of a compound wherein X is H and Y is $-OR^{10}$ or $-SR^{10}$, by treating a compound of formula (IA) wherein X is H and Y is OH, $-OR^{10'}$ or $SR^{10'}$ with a compound $R^{10}OH$ or $R^{10}SH$;

and thereafter, or simultaneously therewith, effecting one or more of the following optional conversions:-

(i) when the compound of formula (IA) is formed, converting it into another compound of formula (IA) having different values of R_2, R_3, R_4, R_5, R_6 and R_7 by treatment with an appropriate reagent and/or under suitable conditions;

(ii) removing any remaining protecting groups;

(iii) when the compound of formula (IA) is formed, converting in into a pharmaceutically acceptable derivative thereof;

(iv) when a pharmaceutically acceptable derivative of a compound of formula (IA) is formed, converting the said derivative into a compound of formula (IA), or a different derivative thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00570

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/40; C07D403/14

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	EP,A,0 397 060 (GÖDECKE AG) 14 November 1990 cited in the application see claims 1,7,8	1-5, 14-15
X	EP,A,0 328 026 (HOFFMANN-LA ROCHE) 16 August 1989 cited in the application see page 9, line 11 - line 18	1-5, 14-15
X	DE,A,3 914 764 (GÖDECKE) 8 November 1990 see page 2, line 66 - page 3, line 2 see page 7, line 22 - line 31	1-5, 14-15

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11 JUNE 1993	01. 07. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	GERLI P.F.M.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	FEBS LETT. vol. 292, no. 1-2, pages 31 - 33 'Effects od Protein Kinase C Inhibitors on Viral Entry and Infectivity' see the whole document	1-17
Y	EP,A,0 384 349 (HOFFMANN-LA ROCHE) 29 August 1990 see claims 18-21	1-17
Y	EP,A,0 470 490 (HOFFMANN-LA ROCHE) 12 February 1992 see claims 1,10,12,13	1-17
T	J.MED.CHEM. vol. 35, 1992, pages 177 - 84 'Inhibitors of Protein Kinase C. 1. 2,3-Bisarylmaleimides' see page 180; table IV	1-17
A	BIOCHEM.BIOPHYS.RES.COMMUN. vol. 171, no. 1, 1990, pages 148 - 154 'K252a is a Potent and Selective Inhibitor of Phosphorylase Kinase' see page 149; figure 1	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB93/00570

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 16 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based upon the alleged effects of the compound/cpomposition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300570
SA 71789

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 11/06/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0397060	14-11-90	DE-A-	3914764	08-11-90
		DE-A-	3942991	04-07-91
		AU-B-	634541	25-02-93
		AU-A-	5466690	08-11-90
		CA-A-	2015996	05-11-90
		JP-A-	2306974	20-12-90
EP-A-0328026	16-08-89	AU-A-	2965889	10-08-89
		JP-A-	1233281	19-09-89
		US-A-	5057614	15-10-91
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		AU-A-	5466690	08-11-90
		CA-A-	2015996	05-11-90
		EP-A-	0397060	14-11-90
		JP-A-	2306974	20-12-90
EP-A-0384349	29-08-90	AU-B-	633051	21-01-93
		AU-A-	5003390	30-08-90
EP-A-0470490	12-02-92	AU-A-	8167291	13-02-92
		JP-A-	4230686	19-08-92

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82